CENTER FOR INDOOR AIR RESEARCH
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APPLICATION FOR RESEARCH CONTRACT

1. PRINCIPAL INVESTIGATOR. Name, title, telephone # and mailing address.

(a) Adolfo Correa-Villaseñor (Name) (b) M.D., Ph.D. (Title) (c) (301) 955-3483 (Telephone number)

(d) Epidemiology (Department) (e) The Johns Hopkins University School of Hygiene (Institution)

(f) 615 North Wolfe Street, Baltimore (Mailing Address) (g) MD, 21205 (State/Zip)

2. PROJECT TITLE. (Do not exceed 75 typewriter spaces inclusive of spaces between words and punctuation.)

Charcoal-smoke and risk of respiratory infections

3. KEY WORDS. Please provide three (3) key words which will be used as reference headings.

Respiratory infections; indoor pollution; charcoal-smoke

4. INSTITUTION. Name and address of institution responsible and accountable for disposition of funds awarded on the basis of this application.

(a) JHUSHPH (Institution) (b) 615 North Wolfe Street (Street Address)

(c) Baltimore (City) (d) MD, 21205 (State/Zip)

5. LOCATION. List location where research will be conducted *if other than institution identified in #4 above.*

(a)

(b)

6. INCLUSIVE DATES and TOTAL COSTS of this specific project related to each 12 month period if more than one year is required to complete project. Summarize from budget page, item 13(j). It must be understood that awards for 2nd and 3rd periods are dependent on Science Advisory Board review and Center approval of continuation application.

	Inclusive Date			Total Cost
(a) 1st 12 month period if required	Feb/1991	thru	Jan/1992	$ 197,510
(b) 2nd 12 month period	Feb/1992	thru	Jan/1993	$ 130,123
(c) 3rd 12 month period		thru		$

7. INSTITUTIONAL OFFICER. Name, title and telephone # of individual authorized to sign for the institution identified in #4 above. It is understood that the officer, in applying for a contract, has read and found acceptable the Center's Management of Research Contracts and Contract Administration Policy.

(a) Alan M. Goldberg, Ph.D. (Name) (b) Associate Dean for Research (Title)

(c) (301) 955-3256 (Telephone) (d) ____ (Signature of institutional officer) (e) 12/4/90 (Date)

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8. AIMS*. Please be specific.

(a) Hypothesis

(b) Objectives

9. SIGNIFICANCE OF PROPOSED WORK*

(a) Background

(b) Literature

(c) Identification of gaps in proposed research area

(d) Project importance

10. PRELIMINARY STUDIES*

(a) Feasibility of proposed research

(b) Qualifications of investigator

11. EXPERIMENTAL PLAN*

(a) Design

(b) Methods

(c) Analysis of data

(d) Interpretation of results

(e) Timetable for the investigation

(f) Literature cited

12. AVAILABLE FACILITIES AND RESOURCES

12A. OTHER SUPPORT

List all currently active and pending support for all key personnel involved in this proposal. Include the source of support, percentage of appointment, dates of project, a brief description of the project and whether it overlaps, duplicates, replaces, or supplements this proposed work in any way.

* Append as much material as required. TYPE, single space, use 8-1/2" x 11" white paper and label each sheet with name of the principal investigator in upper right hand corner and page number at the bottom. Consecutively number each addendum beginning with page 5. Do not insert pages between pages 1 and 6, e.g. 2a, 2b, 3a, etc. include nine copies and an original. If sending photographs, include 2 original sets.
Note: All nine copies *must* be placed in a press board binder per mailing instructions.

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R: REDACTED MATERIAL

13. BUDGET. Detail specific needs for first 12-month period. Estimate category sub-totals for 2nd and 3rd periods, if required. Append justifications.

		$ 1st period	$ 2nd period	$ 3rd period
(a) Salaries, List personnel by name and title. Indicate individuals % time to be spent on this project.		See attached sheet.		
% Professional:	A. Correa-Villaseñor G. Matanoski S. Bowes L. Bautista	REDACTED		
Technical:	K. Thomas V. Cairo Secretary			
Other: *	TBN Data Collectors 4 TBN Env. Data Coll. 5	REDACTED		
*See attached sheet Fringe benefits payable at institution's rate of ** % ** See justification				
	Category (a) Sub-Total	$ 105,429	$ 74,079	$
(b) Consultants (per diem, travel & expenses):				
	Category (b) Sub-Total	$	$	$
(c) Supplies & Expense: Consumables (by category)	Stationery	412	180	
	Software: DBIV	795		
	Air Sampling	8,665	8,665	
Animals and related costs –				
Other expenses (itemize)	Sample shipment	3,765	3,765	
	Arm circumf. tapes	160		
	Thermometers	2,617		
	Office furniture	600		
	Publication costs		420	
	Telephone	120	60	
	Category (c) Sub-Total	$ 17,134	$ 13,090	$
(d) Travel & Expenses:	Air fare	2,000	1,000	
	Expenses	1,500	530	
	Category (d) Sub-Total	$	$	$
(e) Alterations and Renovations				
	Category (e) Sub-Total	$	$	$
(f) Sub-contracts				
	Category (f) Sub-Total	$	$	$

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Category (g) Sub-Total	$ 18,772	$	$
(g) Equipment Kurz 490 Anemometers, 6 ($400/u)	2,400		
Gillian HFS-513a sampling pumps, 12 (856/u)	10,272		
MBO MiniBuck calibrator, 2 ($1,200/u)	2,400		
Gillian Cyclone and filter holder, 10 (70/u)	700		
CompuAdd PC/AT, monitor, printer, 1	3,000		
(h) TOTAL DIRECT COSTS	$ 158,008	$ 104,098	$
(i) Indirect costs not to exceed 25% of the sum of (a) thru (f):	$ 39,502	$ 26,025	$
(j) TOTAL PROJECT COSTS	$ 197,510	$ 130,123	$

14. BIOGRAPHICAL SKETCH of all professional personnel listed in 13(a). Append. Please include the following: Name, title, education; scientific field, major research interest, research and/or professional experience and publications. (Limit list of publications to the 20 most important and/or relevant.)

15. a) Are HUMAN SUBJECTS to be used in this research? X Yes ____ No

If yes, attach Institutional Review Board approval for procedures involving human subjects.

b) Are LABORATORY ANIMALS to be used in this research? ____ Yes X No

If yes, attach Institutional Animal Care and Use Committee approval for procedures involving animals.

16. If you wish to recommend peer reviewers (outside of your institution) for this proposal, please append their names, addresses, and telephone numbers. Recommendations of peer reviewers are not an application requirement.

17. SIGNATURE OF PRINCIPAL INVESTIGATOR: It is understood that the applicant in applying for a Contract has read and found acceptable the Statements of Policy and Terms Under Which Project Contracts Are Made appearing in the application package.

Adolfo Herrera V. Date 12/01/1990

Signature of Principal Investigator

rev. 5/90

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Charcoal Smoke & Risk of Respiratory Infections

NAME	ROLE IN PROJECT 03-Dec-90	01 EFFORT	01 BUDGET	02 EFFORT	02 BUDGET	TOTALS

REDACTED REDACTED REDACTED

REDACTED REDACTED REDACTED

REDACTED REDACTED REDACTED

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RESEARCH ABSTRACT

Title of Project: Charcoal-smoke pollution and risk of respiratory infections.

Investigator(s): Dr. Adolfo Correa-Villaseñor, M.D., Ph.D.
Dr. Genevieve M. Matanoski, M.D., Ph.D.
Dr. Leonelo E. Bautista, M.D., M.P.H.
Dr. Stephen Bowes, Ph.D.

Institution: The Johns Hopkins School of Hygiene and Public Health

ABSTRACT: In the space below, please provide a descriptive summary of your proposed research project.

The purpose of this study is to assess the effect of indoor charcoal-smoke pollution on acute respiratory infections (ARI) in children.

The specific aims of the study are: 1) To assess whether children less than two years old exposed to indoor charcoal-smoke have an increased risk of acute lower respiratory infections (LRI) and acute upper respiratory infections (URI); 2) To evaluate dose-response relationships; 3) To evaluate the relationship between exposure and ARI severity; and 4) To explore the association between ARI and previous episodes of ARI.

The study will be concurrent prospective. Exposed and non-exposed cohorts will be drawn from the Santo Domingo's children population. This population has a high incidence of ARI, a large proportion of exposed children, and low mobility. The study sample consists of 200 children under two years old in each group. The follow-up will last one year. Data on exposure will be gathered by interview and measurements of indoor respirable particle concentration. Data on ARI will be also obtained by examination of the child and interview of the child's mother every two weeks.

The study will provide information on the impact of indoor charcoal-smoke pollution in LRI and URI among children. This information may be useful in selecting preventive strategies for ARI.

Adolfo Correa V.
Signature, Principal Investigator

12/05/1990
Date

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RESEARCH PLAN

8. SPECIFIC AIMS

The overall goal of the proposed study is to examine the relationship between indoor charcoal-smoke exposure and risk of acute respiratory infections (ARI) in children less than two years of age. The major hypothesis being tested is that exposure to charcoal-smoke increases the risk of lower respiratory infections (LRI) and upper respiratory infections (URI) in children less than two years of age. The specific aims are:

1. To assess whether children under two years of age exposed to indoor charcoal-smoke have an increased risk of LRI and URI.

   a. To determine the incidence of LRI and URI in children not exposed to indoor charcoal-smoke.

   b. To determine the incidence of LRI and URI in children exposed to indoor charcoal-smoke.

   c. To estimate the relative risk and the attributable risk of LRI and URI associated with indoor charcoal-smoke exposure.

2. To evaluate dose-response relationships between indoor charcoal-smoke exposure and risk of ARI.

3. To examine the association between indoor charcoal-smoke exposure and ARI severity.

4. To assess whether the risk of ARI in a child is influenced by previous episodes of ARI in the same child.

9. SIGNIFICANCE OF PROPOSED WORK

9.a Background and Literature

Mortality and Morbidity in Developing Countries

Acute respiratory infections (ARI) are a frequent cause of morbidity and mortality among all age groups in the developed as well as the less developed countries. In less developed countries the impact on mortality is more accentuated among children less than five years old. In this age group, ARI are one of the most important causes of death;[1,2] they result in 2.2 million to 4 million deaths annually,[1,3] or 15 to 33% of all deaths in this age group.[1,2] Even in developed countries the mortality burden is high since ARI account for 10 to 15% of all infant deaths.[4] However, in less developed countries the impact is much larger for ARI mortality in children less than 5 years old may be 30 or more times higher than that in developed countries.[4,5] This appears to be the current situation in Latin American countries where death from pneumonia figured among the six leading causes of death at the beginning of the 1980s.[6]

ARI are also a major cause of morbidity. ARI are the most frequent type of self-limited disease in childhood.[1,2] In urban areas the average number of ARI episodes per child per year is between 5 and 8; this figure appears to be slightly lower in rural areas.[3,7] The overall incidence of ARI seems to be similar in both developed and less developed countries but the relative frequency and severity of LRI is very different.[3,8] While the incidence of pneumonia is about 3-4 per 100 children-years in developed countries, it is at least twice as high in less developed countries (7-10 per 100 children-years[8]). These high incidence and mortality ARI rates reflect a substantial burden on the health systems of all countries.

ARI Etiologic Agents.

ARI have a broad spectrum of etiologic agents. Viral infections are considered to play a more important role than bacterial infections, accounting for 95% of URI and a similar but lower proportion of LRI.[9] Respiratory syncytial virus (RSV), parainfluenza, influenza and adenovirus are the most frequent viral etiologic agents of LRI. These same viruses together with rhinovirus and coronaviruses cause the majority of URI. Among the most important bacterial agents of LRI are Streptococcus pneumoniae, Hemophilus influenzae, Staphylococcus aureus, Streptococcus pyogenes and Mycoplasma pneumoniae. Bacterial URI are caused by the same agents causing bacterial LRI as well as

others like Bordetella pertussis and Corynebacterium diphteriae. Important variations in relative frequency in these agents occur in different populations and age groups.

Bacterial pneumonia tend to be more frequent in less developed than in more developed countries. Several studies of etiological agents of pneumonia among children from less developed countries and who had not received antibiotics are consistent in reporting positive bacterial cultures in about 60% of the cases.[3] On the other hand, a study of the same issue carried out by Rapkin in New Jersey[10] identified a bacterial cause in only 11.1% of the pneumonia cases. About 80% of all bacterial pneumonia are due to Streptococcus pneumoniae and Haemophilus influenzae.[3]

. Strategies for ARI Control

Primary prevention of ARI includes immunization, chemoprophylaxis, and modification of risk factors. Secondary prevention is based primarily on early case detection and treatment with antibiotics and aimed at reducing mortality from pneumonia.

At the present time the options available for vaccine prevention of ARI are very limited. The vaccines included in the WHO Expanded Program of Immunization (i.e. measles, pertussis, and diphtheria vaccines) are very useful in providing protection against some of the more virulent respiratory pathogens; however, they do not protect against today's more common pathogens. Polyvalent pneumococcal vaccines as well as Haemophilus influenza polysaccharide vaccine have been proved efficacious in older individuals but not in children younger than 18 months, an age group with the highest morbidity and mortality.[1,8,11] Although influenza virus vaccines have been found effective, they have to be administered yearly and are prohibitely costly for less developed countries.[2,8,12]

Chemoprophylaxis can be used to prevent infections by influenza virus, rhinoviruses, and coronaviruses. However, massive use of chemoprophylaxis for preventing ARI is fraught with many difficulties.[8]

Since vaccine development and use do not offer an effective short term solution for the problem of ARI prevention in less developed countries, identification of modifiable risk factors becomes an important ARI research strategy. Factors known or suspected to influence the risk of ARI in children include age, sex, low birth weight, exposure to outdoor air pollution, exposure to indoor air pollution from passive smoking or burning of biomass fuels, crowding, breast feeding, level of nutrition, socioeconomic status, and meteorologic conditions.[13,14] Several of these factors

are clearly correlated and their individual effects on ARI risk have not been completely sorted out.

Risk factors amenable to modification include exposure to outdoor air pollution, exposure to indoor air pollution from passive smoking or burning of biomass fuels, low level of breast feeding and low level of nutrition. Efforts to improve the levels of the latter two factors are being made in various locations, and steps to reduce indoor air pollution from smoking or cooking with biomass fuels have been recommended in areas where it is a potential problem. However, recommendations with regards to burning of biomass fuels for heating or cooking have not been widely implemented. Part of the reason for this situation may be that the actual independent effect of burning or biomass fuels on ARI risk has not been clearly established.

9.b Gaps in Proposed Research Area

Biofuel-smoke and ARI risk

A primary source of indoor air pollution, in addition to cigarette smoke, is the combustion of biomass fuel. The most commonly used biofuels are wood, dung, crop residues and wood-charcoal.

Although few studies have been reported on the effects of particular components of biofuel smoke, the similarity between wood smoke and cigarette smoke suggests similar health effects from wood smoke.[15] The non specific defense mechanisms of the lung are based on aerodynamic filtration, mucociliary clearance and in situ detoxification. Aerodynamic filtration prevents the air exchange region of the lung from being exposed to the environment. Visible airborne particles and those about 10 μm or more in diameter are filtered out at the nose, but smaller particles can reach the bronchi and those of 3 μm or less can reach the alveoli. Since most biofuel smoke particulate are less than 3 μm in diameter, they can easily reach the deepest portions of the respiratory tract and alter other non specific defense mechanisms.

Mucociliary transport removes inhaled particles from the air tract. This mechanism operates at the ciliated portion of the air ways (nose to alveoli). Particles are entrapped on the mucus and moved upward to the pharynx by the ciliated epithelium. Several biofuel combustion byproducts reduce the clearance capability of the lung by impairing mucociliary activity. Particular effects are irritation to the mucosa, coagulation of mucus, cilia toxicity, inhibition of the cilia activity and increased attachment of bacteria to the respiratory mucosa.[16-18]

The reduction of the clearance mechanisms of the lung results in an increased residence time of inhaled particles such as airborne microorganisms. The larger residence time favors the microorganisms growth and the development of infection.

In situ detoxification is the main non-specific defense mechanism in the deepest, non-ciliated portions of the respiratory tract. This mechanisms is based on the phagocytic action of resident macrophages enhanced by circulating polymorphonuclear leukocytes and the action of immune factors such as lysozyme and interferon which suppress the growth of bacteria and viruses. Biofuel smoke components, particles as well as gases, reduce the macrophage bactericidal activity and the interferon production.[19,20] The ability of the lung to effectively cope with challenging microorganisms is impaired and the likelihood of infection increases.

Several studies on the respiratory effects of wood-smoke have been carried out in different populations. Although some studies suggest an effect of wood-smoke indoor pollution in chronic non infectious lung disease in adults,[21-25] and also an effect in acute respiratory infections in children, the evidence is far from conclusive. A number of studies using different designs have shown an increase in the risk of ARI or respiratory symptoms among children exposed to wood-smoke.[26-28] On the other hand, other studies have failed to demonstrate such a wood-smoke effect[29-31](See addendum #1). Some of these studies have focused on school age children, who are very different from children less than two years of age because their risk of ARI is much lower and their level of exposure much less due to their pattern of daily activities. In addition, problems of small sample size or lack of adjustment for potential confounders such as parental smoking, age and breast feeding, however, have raised questions regarding the validity or magnitude of the estimates of effect in these studies.

The pollution produced by wood-charcoal burning is different from that produced by wood burning. Charcoal results in relatively lower levels of total suspended particles but a higher concentration of CO.[15] Since major pollutants are still produced by wood-charcoal burning, charcoal-smoke exposure could result in similar health effects as those postulated for wood-smoke.

Hypothesis

Although the results of the various studies of the association between biofuel smoke and ARI risk in children may be inconclusive, the available evidence does suggest a possible role for charcoal-smoke in the susceptibility to and severity and duration of ARI.

Like wood smoke, charcoal smoke contains several major pollutants including carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), suspended particulate matter, aldehydes and polycyclic organic materials.[15,32,33] Of these, NO_2, SO_2, aldehydes, phenols and toluene have been shown to be air tract irritants,[16,17] and suspended particulate matter (SPM) can adversely affect antibacterial defense mechanisms of the lung, such as mucociliary transport, macrophage phagocytic function[19] and interferon production.[20]

Exposure to charcoal smoke may result in similar health effects postulated for wood smoke. With defenses and clearing mechanisms impaired by SPM, infections are not only more likely to occur, but the infections that do occur are more likely to extend and involve various regions of the respiratory tract and result in illnesses that are more severe and/or of longer duration.

9.c Project Importance

Wood-charcoal Smoke and ARI Risk in Santo Domingo

The current situation of outdoor air quality in Santo Domingo, Dominican Republic, has not been well described. Outside the occupational setting, very little information is available on exposure to air pollutants. However, as Santo Domingo is not a highly industrialized city and most of the industries are located outside the city, it is reasonable to assume that the major source of outdoor air pollution within the city is the combustion of fossil fuel from vehicles. Levels of outdoor air pollution have never being high enough as to generate health concerns in the community.

Indoor sources of air pollution are similar to those in other urban populations. Since in some 50% of all households there is at least one person who smokes, this may be the main source of indoor pollution. Another important source is the combustion of fuels used for cooking. For cooking, about 80% of all households depend on propane gas, a known source of gases like NO_2 and SO_2; the rest of the households use biofuel mass, mostly wood charcoal. Another occasional indoor pollution source is the burning of candle lights or kerosene gas for illumination purposes during the night.

In Santo Domingo the incidence of ARI is similar to that in other less developed countries. In 1987, the average number of episodes among children less than five years old was estimated at 5.5 per child per year.[34] A more recent estimate of the ARI incidence in children under 2 years of age is of 10.9 episodes per child-year (see Addendum #2). Since ARI are not conventionally

reported to health departments and there are no longitudinal surveys to estimate incidence of LRI, only indirect estimates of LRI incidence are available. Given the above estimate of ARI incidence, the fact that in developing countries 3% of all ARI cases occur among infants and 1.5% of all ARI cases occur in children less than 2 are LRI,[35] we estimate that the overall incidence of LRI in Santo Domingo is 25 cases per 100 children-years (see Addendum #2). This estimate is similar to that reported for other developing countries.[3]

In the National District of the Dominican Republic, the political region where Santo Domingo is located, pneumonia is the fourth cause of death in infants and the second in children 1-4 years old.[36] At the Robert Reid Cabral Children Hospital (RRCCH), the major pediatric center in Santo Domingo, ARI are the second cause of death[37] and have a case fatality ratio of 4-6%.[38]

ARI are currently the most frequent cause of outpatient visits in Public Hospitals. At the RRCCH, ARI account for 21% of all clinics visits,[39] and pneumonia is the first cause of hospitalization.[38]

Proposed Study

The proposed study aims to assess the relationship between exposure to indoor charcoal-smoke and ARI risk and severity in a cohort of children under 2 years of age in Santo Domingo, Dominican Republic. Follow up of the cohort will be active, with questionnaire data on exposure and outcome obtained by means of bi-weekly home visits. Ambient measures of particulate will also be obtained in the households on a sample of the visits. At each home visit the study subjects will also be examined for evidence of ARI by a nurse.

Children under 2 years of age in Santo Domingo comprise an ideal population in whom to evaluate the charcoal-smoke-ARI relationship for the following reasons.

1. About a fifth of the households in Santo Domingo neighborhoods use wood-charcoal as the primary biofuel for cooking, resulting in a substantial number of children with potential exposure to charcoal-smoke.

2. Sources of outdoor air pollution in Santo Domingo are few, the main one being fossil fuel combustion from automobiles.

3. As they stay indoors most of the time, children under 2 years have limited exposure to outdoor air pollution.

4. Such children are not directly exposed to tobacco smoke; their main exposure to respirable particles comes from indoor air pollution.[40]

5. Since they stay indoors most of the time and they are likely to be present in the vicinity where the cooking takes place, children under 2 years have potential exposures to significant levels of charcoal-smoke with every cooking activity.

6. For a given indoor ambient concentration, penetration of particles to the deepest regions of the lung, and therefore exposure dose, can be even greater in children under 2 years than in adults since their lung volume in relation to body size is at least twice that in adults, their respiratory rates are higher,[20] and they stay indoors more.

7. Children under 2 years of age have a higher risk of ARI and of LRI in particular, which will allow evaluation of the study hypothesis over a shorter period of follow up.

Implications for Prevention

ARI represent a significant cause of morbidity and mortality in young children. That children with ARI early in infancy have an increased risk of subsequent ARI suggests that either the same predisposing conditions persist or that the exposure induced impairment of defense mechanisms may not be as readily reversible as suspected. Such chronic effects could lead to periods of inadequate nutrition, which, in turn, could exacerbate already present nutritional problems and increase the risk of subsequent ARI.

In communities where burning of biomass fuels prevails and ARI prevention resources are limited, a practical public health research strategy is to define the individual role of pollutants from burning of biomass fuels on ARI risk and severity. This approach may facilitate identification and prioritization of appropriate intervention measures.

The proposed study intends to shed light on the effect of charcoal smoke pollution in ARI risk in children. Findings of this study may help in the process of selecting strategies for ARI prevention in Santo Domingo, a high incidence area. Even if the

relative risk associated with charcoal smoke pollution is not very high, the preventive fraction could be substantial given the high frequency of exposure and disease incidence.

In a recently completed survey of a systematic sample of four Santo Domingo neighborhoods (n=1,333), the prevalence of exclusive use of charcoal burning was found to be 21%. If the relative risk of ARI associated with charcoal-burning exposure is in the range of 1.5 to 2.0, the attributable risk will be between 10 to 17% (i.e. $[(0.21x0.5)/((0.21x0.5) + 1)] = 0.10$). That is, if the exposure prevalence is of 21% and the relative risk is 1.5-2.0, 10 to 17% of all ARI cases might be prevented by elimination of such an exposure.

Santo Domingo is the most developed area of the Dominican Republic and, as such, has an exposure prevalence well below that found in more rural areas. The potential for prevention in the rural areas, therefore, might be even higher. Simple actions like modifying stove design or increasing indoor ventilation, for example, could result in the prevention of a large number of cases. As charcoal smoke indoor pollution may be more modifiable in the short term than factors such as malnutrition and parental smoking, a clear description of charcoal smoke effects would be helpful in defining preventive strategies for ARI.

10. PRELIMINARY STUDIES

As part of its curricular activities, the Public Health Department of the Autonomous University at Santo Domingo (AUSD) carries out one or two annual surveys on different health problems in Santo Domingo. These surveys have resulted in extensive experience and detailed information needed to support community studies. In all of these surveys the cooperation of the population has been very high.

One of the co-principal investigators (L.B.), a faculty member at AUSD, has been involved in many of the above surveys, including the conduct of a survey of diarrheal disease morbidity in a sample of more than 7,000 children.[41] In addition, he recently conducted a pilot survey of selected Santo Domingo households to obtain estimates of ARI frequency, type of fuel use for combustion in the household, crowding, and parental income, education and smoking habits.

In this last survey, more than two thousand children under five years of age were selected by systematic sampling of 1,333 households in several neighborhoods. Thirty four percent of the children (459) were less than two years old. The typical household was found to have two bedrooms and a living room; the kitchen was under the same roof but usually in a separate room. However, in 20% percent of the households, cooking activities were carried out either in a bedroom or in the living room. Cooking was found to be usually carried out three times a day for an average of 3.5 hours per day. Twenty three percent of the children under 2 years of age were found to live in households where the energy source for cooking was burning of wood charcoal.

In the same survey, ARI episodes were identified by maternal report of ARI manifestations in the child during the week previous to the survey. The ARI incidence rate was found to be 21 per 100 children-weeks (10.9 episodes per child per year). LRI episodes identified by physician diagnosis resulted in an incidence estimate of 27 cases per 100 children-years.

For those children who attended a physician during the previous week, the level of agreement between our questionnaire-based case definition and that based on the physician diagnosis was determined. There was 94.6 percent agreement, with 82% of the agreement being above chance (Kappa statistic).

Children living in households that used wood charcoal for cooking (i.e. potentially exposed to charcoal smoke) were found to be 1.2 times more likely to have an episode of ARI during the previous week (95% confidence interval [CI]: 0.7 - 2.2).

Adjustment by age, sex, number of children less than 5 in the household, mid upper arm circumference (MUAC) and maternal education had no material effect on the crude odds ratio.

The median number of people per household was found to be 6 (mid-fifty=4,7). The mean sleeping density (crowding) was 3.4 individuals/room for households using propane gas for cooking and 4.3 for households using wood charcoal.

The prevalence of malnutrition, as defined by MUAC, was 9%. Exposed children were on the average 1.12 times more likely to be undernourished than non-exposed children (95% C.I.= 1.01, 1.24). However, children with low MUAC were similar to those with normal MUAC in terms of incidence of ARI. Birth weight was not found to be associated with the type of fuel used for cooking in the household.

Families using propane gas for cooking were found to have a higher average monthly income than families using wood-charcoal, but there was a high degree of overlap between both income distributions. A similar situation occurred with maternal education.

11. EXPERIMENTAL DESIGN AND METHODS

11.a Design Overview

A concurrent prospective design will be used. Practical and methodological considerations suggest this design as the most appropriate for studying ARI and time-dependent risk factors. Given the high incidence of ARI, the follow up period required to observe sufficient cases in a defined cohort is relatively short. Also, in a cohort study standardized, repeated measures can be obtained on subjects for both outcome and exposure variables. These measurements facilitate the assessment of the relationship between ARI and changes in environmental factors. A case-control design would be more prone to exposure misclassification errors. In addition, ascertainment of a representative sample of ARI cases for a case control study would be difficult given the various selection factors that determine health care seeking behavior and access for cases of ARI.

11.b Methods

11.b.1 Study population

The study population will be comprised of a sample of children less than two years of age, living in Santo Domingo, Dominican Republic, during 1990-1991. Given the high incidence of ARI and the prevalence of cooking with wood charcoal in Santo Domingo, this population offers a unique opportunity for studying charcoal smoke health effects. In addition, this population is not very mobile; the small migration that occurs does so mainly toward the city. This latter factor and an excellent degree of cooperation obtained in previous prevalence and cohort studies[34,41] suggest that a follow up study in this population is feasible.

11.b.2 Eligibility criteria

In an effort to maintain ready accessibility to the study subjects and their birth data, insure a sufficient number of cases over the study period, minimize losses to follow-up during the study period, and minimize misclassification of exposure status due to exposures from other sources, the following subject eligibility criteria will be observed. To be included in the study, a child at the time of recruitment must:

1. Be a resident of Santo Domingo;
2. Have been born in a Santo Domingo medical institution;
3. Be less than two years of age; and

4. Live in a household whose members do not smoke or use the home for sanding, welding, manufacturing or arts and crafts work.

Restricting the study population to residents of Santo Domingo minimizes the amount of field staff travel in going from the University to the homes of the study subjects and from home to home. This feature is essential for the successful completion of the proposed repeated measures.

One of the potential confounders for which this study will control is birth weight. Data on this variable are likely to be more accurate if obtained from birth records than by interview. Restricting the study population to children born in Santo Domingo will facilitate the retrieval of such data. Few exclusions are expected on this basis, since most children residing in Santo Domingo were born there.

Focusing on children under 2 has several practical advantages. First, since they stay indoors most of the time, children under 2 have potential exposures to significant levels of smoke from charcoal-burning with each cooking episode. Second, such children are more likely to stay indoors and in the same room; indirect measures of exposure, therefore, are likely to be more accurate and reliable. Third, children under 2 usually are not directly exposed to tobacco smoke or to other sources of air pollution; their main exposure to respirable particles comes from indoor pollution.[40] Exposure misclassification errors due to false negative exposures (from other sources) are likely to be smaller. Fourth, the high incidence of ARI in children under 2 reflects sufficient opportunities for exposure to respiratory pathogens, critical for evaluating the effect of charcoal-smoke exposure on the risk of ARI. Fifth, since validity of the LRI diagnostic criteria is better for younger children (see 11.b.5), outcome misclassification errors will be minimized. Lastly, children under 2 are generally healthy. Conditions that might interfere with an accurate diagnosis of ARI (e.g. asthma or chronic bronchitis) or lead to losses to follow-up during the study period, from prolonged or recurrent hospitalization or death (e.g. bacterial meningitis, dehydration, neoplasms), are rare. Nevertheless, during the recruitment interview, each mother will be queried about history of such medical conditions among her children. Given that in Santo Domingo health care is free, health service utilization tends to be high. Thus, children with any of the above conditions are usually seen at a medical center and their mothers are likely to remember such visits to the doctor. Children identified as having such conditions during the recruitment interview of the mother will be excluded.

Identification and exclusion of households where members either smoke or are involved in activities likely to generate significant amounts of dust is important. Such potential exposures might be more difficult to measure and their confounding effects would be difficult, if not impossible, to control in data analysis.

11.b.3 Enrollment

The approach to study population selection will aim at making the two study groups different with regard to potential exposure to charcoal-smoke. This approach will also aim at making the two study groups similar in terms of potential confounders or in the degree of within-group heterogeneity of such confounders.

Results from the pilot survey (see Section 10 and Addendum #2) indicate that cooking without charcoal is four times as common as cooking with charcoal, neighborhoods with a high proportion of charcoal-using households also have sufficient numbers of non charcoal-using households and that the two types of households in such neighborhoods exhibit similar distributions of potential confounders, including socioeconomic status. This suggests a practical approach to selection of the two groups, from the same high charcoal-using neighborhoods and based on potential exposure status; it also suggests that potential residual confounding can be properly accounted for in the analysis.

Based on the recent pilot survey, Santo Domingo neighborhoods have been classified by the proportion of households where cooking is based on charcoal-burning. There are approximately 300,000 households in Santo Domingo, distributed among 100 neighborhoods. About 20% of these can be considered as high charcoal-users. Up to four neighborhoods in the top quintile of charcoal-users will be selected randomly for a survey that will identify households with eligible subjects.

Households in the above selected neighborhoods will be surveyed with regard to the number of eligible children and the main source of energy used for cooking. For every household with an eligible child, that uses charcoal for cooking and that is willing to participate ("with potential for exposure"), a household in the same neighborhood, with an eligible child, that uses propane gas or electricity for cooking will be recruited ("with no potential for exposure"). Households where more than one type of fuel is used are extremely rare and will not be considered as eligible. The recruitment of subjects into the two comparison groups for follow up will be done concurrently, and carried out until the required sample size is reached.

In these households with more than one child under 2, the youngest child will be selected for follow up. This approach will result in a sufficient number of children in each exposure group, in the age group with the highest risk of ARI, a larger number of child-years of follow up and, therefore, higher statistical power.

11.b.4 Exposure Definition

Two types of exposure measures will be used: one based on reports of type of cooking fuel used; another based on ambient measures of indoor air pollution.

Cooking fuel reports

At each of the bi-weekly follow up visits, mothers will be interviewed regarding cooking fuel type, cooking activities and the child's activities during the previous day. Reports on the type of cooking fuel will be used to classify subjects as exposed or not exposed. A child living in a household where wood charcoal is the only reported source of energy for cooking purposes will be considered as having potential charcoal smoke exposure. A child living in a household where propane gas or electricity is the only reported source of energy for cooking will be considered as having negligible potential charcoal smoke exposure. Households where wood charcoal and other types of fuel are used are rare and will not be included in the study population.

Since potential exposures can change qualitatively over time (i.e. a household could change its use of cooking fuel during the follow up period, from wood charcoal to gas for instance), and this change could vary between households where such a change occurs, the exposure classification system will include an element of follow up time. That is, at each of the bi-weekly follow up visits, mothers will be interviewed regarding cooking activities and the child's activities during the previous day. Data to be collected on such activities will include amount of wood charcoal used, type of wood, type of food prepared, the amount of time that the stove was used, the room where the child spent his time during the cooking, and the child's activities at the time of the cooking. These data will be used to create an index of potential exposure that is time-dependent.

For every follow up visit, the cooking and child activity data will also be used to develop two forms for the potential exposure variable: qualitative and semi-quantitative. The qualitative form will consist of two exposure levels (i.e. yes or no); the semi-quantitative form will be ordinal with the ranking of the various

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levels defined by an index of the amount of wood charcoal used, location and activity level of the child at the time of cooking.

Environmental Exposure Measures

Environmental exposure assessment will also be carried out by means of indoor air sampling. Many different substances can be used as indices of smoke pollution exposure: benzo(a)pyrene, carbon monoxide, nitrogen oxides, sulfur oxides or respirable particles.[15,42] Of these components, NO_2, SO_2 and air particulate are the ones most likely to increase susceptibility to ARI in children. However, the evidence for an effect of these gases on respiratory function and respiratory diseases is not consistent[43,45] and their concentrations in smoke from wood fire are low.[15,46] Since households using propane gas, a source of NO_2, will be used as control group, measurements of this gas concentration will be taken in both study groups as a way of evaluating its role as a confounder.

Particulate have been used frequently as an indicator of smoke and other forms of pollution.[32,47-49] Health effects of particulate depend on the chemical composition and physical characteristics of the particles, particle size being one of the most important ones. Particle size influences penetration and deposition of particulate in the different areas of the respiratory tract. Three respiratory areas have been defined corresponding to available techniques for sampling and collecting particles of different sizes. Accordingly, three aerosol mass fractions have been recommended for particle size selective sampling.[50-51] These three regions and particle sizes are:

Head airways region (nose to larynx): Inspirable Particle Mass (IPM), defined as those 15-100 µm;

Thoracic airway region (trachea to bronchioles): Thoracic Particle Mass (TPM), defined as those < 10-15 µm (currently named as RP); and

Pulmonary Region (respiratory bronchioles to alveoli): Respirable Particle Mass (RPM), defined as those < 2.5, 3.0 µm (currently named as PM2.5).

These three regions correspond closely to the anatomic division used for classifying ARI (LRI and URI). Although the IPM fraction of an aerosol is likely to cause health effects at the head airway region, it can not be used in this study to assess possible associations with URI as the technology for measuring IPM is not well developed.[52] However, as most of the particulate from

biofuel smoke are below 3.2 µm,[15] such particulate are not likely to contribute significantly to the IPM fraction.

The parameter to be measured in this study is the RP air concentration. Since these particles deposit mainly in the thoracic and pulmonary airway regions, RP is relevant to the effects this study proposes to evaluate. RP may not be as relevant for URI as it is for LRI, for this particle fraction does not have a high deposition rate in the head airways and the clearance half-time for particles deposited in this region is fast, in terms of minutes.[53] However, in instances where exposure is prolonged or repeated, it is possible for RP to affect the risk of URI.

Possible limitations of the above method are as follows. The above criteria for particle-size selection in exposed healthy adult workers may not reflect the distribution of sizes of particles that are likely to deposit in the smaller airways of children. Nevertheless, the RP fraction includes those particles which penetrate the child's thoracic airway region (see II.b.9).

Charcoal-smoke is not the only indoor source of particles; combined with tobacco smoke, however, it can be considered to be the principal indoor source of particles. Exclusion of households of smokers in this study should improve the correlation between RP particles and potential exposure to charcoal-smoke.

Although personal sampling is the best method for measuring individual exposure to air particulate, adequate instruments for using such a method in children are not available. Correlations between measurements by personal sampling and indoor exposure to RP have been strong for some groups of people.[54] For relatively well ventilated households, however, estimates of personal exposure from area measurements are more problematic. The sampling schedule has to take into account the different sources of variability in particle concentration.

Indoor smoke-derived particle concentration can exhibit diurnal, day-to-day and seasonal variation. Diurnal and day-to-day variations in smoke-derived particle concentration are mainly due to cooking behavior; seasonal variation is due primarily to temperature and humidity conditions. As carrying out individual daily households particulate measurements throughout the year is not feasible, a sampling strategy has been selected to account for the different sources of variation.

In Santo Domingo there are two major weather seasons, a high temperature high rain season (May to October) and a low temperature low rain season (November to April)—See addendum #3—. Therefore, sampling will be done during these two seasons. Particle

concentration measurements will be carried out during January-March, first weather season, and July-September, second weather season, on three randomly selected days at each selected household. On each of these days, the sampling device will be placed for a 12 hour period in the same area of the household where the child usually spends his time during the cooking hours and at the breathing height of the child (see II.b.8). Information gathered during the initial interview regarding such an area will help to identify where to place the air pump. Data on household variables likely to be associated with the aerosol concentration will be collected at each sampling occasion. Such data will include amount of wood-charcoal used for cooking, type of wood, type of food prepared, and frequency and duration of stove use.

Although the above sampling area may vary from household to household, for a given child such an area is likely to reflect the child's breathing zone concentration better than a 'standard" location in all households. Assuming that a child's usual location can be reliably ascertained, this approach should result in less exposure misclassification. An assessment of the validity of this assumption will be made in the first few home visits. If the location of the child at the time of cooking varies, then an alternative approach will be considered for all children (e.g. sampling near the stove and in other rooms in the house).

A nominal dose for each child will be estimated based on the ambient measures. Such an estimate will be a function of the particulate concentration, the age-specific normal respiratory rate[55] and activity level of the child at the time of cooking.

11.b.5 Outcome Definition

Information on the presence of signs and symptoms of respiratory disease in a child will be ascertained by a trained field health worker at each biweekly home visit. At each such visit, using a standardized structured questionnaire the field health worker will query the mother/care taker about the occurrence of and visits to a physician for any respiratory signs and symptoms in her child during the preceding two weeks. The field health worker will also examine the child for evidence of specific symptoms of respiratory illness. Such examination will consist of checking the child's respiratory rate and rectal temperature, and auscultating the child's chest.

An incident case of ARI will be defined as a child who during a follow up visit is either:

a. reported by his/her mother/care taker to have had during the preceding two weeks a clinical condition characterized by at least one of the following:

   1. Cough for 2 or more days;
   2. Ear discharge of any duration;
   3. Runny nose of any duration combined with fever (>=38°C) or cough;
   4. Fever (>=38°C) combined with fast or difficult breathing;
   5. Physician diagnosis of pneumonia, bronchiolitis, bronchitis, tracheobronchitis, pharyngitis, tonsillitis, sinusitis or ear infection; or

b. found by the field health worker to have at least one of the following:

   1. Ear discharge;
   2. Runny nose combined with fever (>=38°C) or cough;
   3. Fever (>=38°C) combined with a respiratory rate over 50/min, chest retractions, rales, stridor, wheeze or cyanosis.

A case of LRI will be defined as a study subject who during a follow-up visit is either:

a. reported by his/her mother/care taker to have had during the preceding two weeks an episode of ARI characterized by at least one of the following:

   1. Fever (>=38°C) combined with fast or difficult breathing;

2. Physician diagnosis of pneumonia, bronchiolitis, bronchitis or tracheobronchitis; or

b. found by the field health worker to have fever (>=38°C) combined with a respiratory rate over 50/min, chest retractions, rales, stridor, wheeze or cyanosis.

Those cases of ARI which do not meet the criteria for the LRI definition will be considered as URI. Determination of whether a child had an episode of ARI and of which kind will be done once all the relevant data have been collected and based on the above criteria.

Ascertaining ARI episodes by means of frequent home visits where inquiry is made about the presence of symptoms and their duration is a technique commonly used in epidemiologic studies of ARI.[35,56-62] Maternal identification and recall of difficult breathing (i.e. chest retractions) can be facilitated by means of pictorial representations during the interview. Rapid respiratory rate as well as chest retractions, either reported by the mother or ascertained by a field health worker, have been found to be strong predictors of LRI.[35,56-59] Combinations of the above clinical signs results in high sensitivity and specificity for LRI in children brought to the hospital with ARI as well as in children enrolled in a community based cohort study.[35,59] For instance, Campbell at al. report values over 90% for sensitivity and specificity for combinations of respiratory rate over 50/min. and chest indrawing as a definition of LRI; such a definition allowed these investigators to readily differentiate between LRI and URI[57] (See addendum #4). The sensitivity and specificity for these criteria are even better among younger children.[57,59]

Presence of fever as well as duration of symptoms are important features for distinguishing respiratory infections from episodes of simple irritation of the airways as might occur with exposure to air pollution. Given the short period of recall required (i.e. two weeks), duration of symptoms is likely to be reported accurately. Assessment and recall of fever without a thermometer reading, however, are likely to be fraught with errors. Accordingly, to improve the accuracy of fever reports, mothers/care takers will be provided with digital thermometers at the beginning of the study and instructed on their proper use by the field health worker. To assess the accuracy of maternal/care taker reports of fever, at randomly selected visits readings on the child's temperature will be obtained by both mother/care taker and field health worker and compared.

The above case definitions represent a reasonable ballance between high sensitivity and high specificity. That is, most incident cases of pneumonia, bronchiolitis, bronchitis or tracheobronchitis will be detected and classified as LRI cases. Similarly, most incident cases of the common cold, tonsillitis, pharyngitis, otitis media or sinusitis will be detected and classified as URI cases.

Since the prevalence of asthma and cardiovascular disease in children under 2 is very low, the probability that incident cases of such chronic disorders might be misclassified as ARI (i.e. false positives) in this study is very small. In any case, the follow up of study subjects in this study will allow identification of such cases (i.e. non resolving, frequent or subsequently diagnosed as having a chronic condition) and an estimation of the error due to this type of misclassification.

Subclinical ARI cases will be missed by the above case definition (i.e. false negatives). However, as such subclinical cases generally are not at risk for significant morbidity or mortality, assessing the contribution of charcoal-smoke exposure to their etiology does not have the same public health priority as for those exhibiting more signs and symptoms.

Among the ARI cases in the study, some of the mild cases of LRI may be misclassified as URI; similarly some of the more symptomatic cases of URI may be misclassified as LRI. To control for the possibility of this type of misclassification, analysis for each type of outcome will be stratified by severity.

All ARI episodes occurring during the follow-up period will be considered as outcomes for analysis. In instances where a child has both URI and LRI, however, only LRI will be counted; also URI episodes which progress to LRI will be counted as LRI.

Consecutive episodes of ARI occurring in the same child will be considered as independent when they are separated by three or more days without symptoms. The period of duration of the ARI episode plus the ensuing three days symptom free period will be counted as person-time not at risk regardless of the type of ARI episode.

Other endpoints to be considered will be severity of the LRI episodes and mortality. Definition of severity will be made at the time of analysis and will be based on the type of symptoms, duration of symptoms, and need for and duration of hospitalization.

11.b.6 Control Variables

To be a confounder, a variable must be associated with both the outcome and the exposure of interest without the confounder being part of the causal pathway. Several variables have been previously reported as being associated with ARI risk and/or with socioeconomic status and, consequently, with the potential for exposure to charcoal-smoke in this study. These variables include age, sex, birth weight, number of siblings, ages of siblings, crowding, breast feeding, nutritional status, socioeconomic status, previous episodes of ARI and passive smoking.

Confounding by smoking will be controlled by excluding households with smokers. Given that two comparison groups for this study will be selected from the same neighborhoods, confounding by socioeconomic status is extremely unlikely (see Section 10 and Addendum #2 regarding the overlap of the distributions of the two groups on socioeconomic status). Nevertheless, evaluation of any potential residual confounding by socioeconomic status will be carried out through stratification and multivariate methods.

Potential confounding by ethnicity is not an issue in this study. Historically, Santo Domingo has been a 'melting pot' of different nationalities. There are no race or ethnic groups; distinction in terms of race or ethnicity is impossible for most, if not all, members of the population. Although neighborhoods may exhibit some segregation in terms of socioeconomic status, there is no discernible concomitant race/ethnicity segregation.

Potential confounding by breast feeding, nutritional status, birth weight and crowding will be evaluated in this study. Data on breast feeding, as most of the data in this study, will be collected prospectively and at frequent intervals (1 or 2 months). Each child's breast-feeding status for a given interval will be categorized according to his/her reported feeding method following the classification proposed by the World Health Organization.[63]

Nutritional status will be evaluated by anthropometric measurements. The measure of nutritional status to be collected on each child is the mid-upper arm circumference (MUAC). For children 1-5 years of age MUAC has been successfully used as an indicator of protein-energy malnutrition.[64-71] This indicator has been shown to correlate closely with weight-for-height, a measure used to detect current malnutrition. A MUAC value between 12.5 and 13.5 cm indicates moderate malnutrition and less than 12.5 cm severe malnutrition.[71] MUAC has been used as a tool for evaluating nutritional status in prevalence studies of children 1-5 years of age as the arm circumference remains almost constant for this age range allowing the use of standard cut-off points to identify

moderate and severe malnutrition. More recently, MUAC has been found to be a very good indicator of nutritional status and predictor of high risk of death in children under 2 years of age, provided that different standard cut off points are used and reliable age data are available.[72-74] MUAC measurements will be obtained by the field health worker on each child on a monthly basis.

Birth weight data will be obtained during the baseline interview of the child's mother. Although accurate recall is potentially subject to some error, in the recent survey conducted in Santo Domingo only 6 of 472 mothers of children under 2 reported lack of knowledge about the child's birth weight (see Addendum #2). Nevertheless birth weight reports will be validated through reviews of hospital birth records. Worth noting is that while hospital records may not be available for common conditions like respiratory infections, records of child deliveries are routinely kept. Three medical or master of public health students from AUSD will be reviewing the birth records as part of thesis research projects required of their degree programs.

Other variables on which data will be obtained by interview of the mother/caretaker include age, sex, number of siblings, ages of siblings, crowding (average number of household members sleeping per room), potential exposure to passive smoking and respiratory symptoms in siblings and parents. For potential exposure to passive smoking and parental respiratory symptoms data will be obtained at baseline and every follow up visit; for the other variables data will be obtained at baseline and at the end of follow up.

As nutritional status and respiratory symptoms in siblings and parents may represent effects or co-outcomes of ARI, they will be handled differently in the analysis.

11.b.7 Data Collection and Follow Up

Overview of Follow Up

As the various independent health care systems in the city do not have adequate information systems to guarantee an appropriate case detection through them, and the demand of medical attention for mild and moderate cases of ARI may be very low, passive follow up is likely to result in significant under-ascertainment of cases. The proposed follow up, therefore, will be active. Information on presence of symptoms and signs of ARI in each child will be obtained bi-weekly by interview of the mother/care taker and

physical examination of each child by a trained field health worker.

Data on changes in exposure and control variables will be gathered during the child health evaluation. Quantitative assessment of exposure will be done 2 times during the year (January-March and July-September) for three randomly selected days as indicated in the Exposure Definition Section (11.b.4).

The follow up will be for one year from the time of enrollment.

Personnel

At the initial phase of the study a team of 5 interviewers will be hired to gather data to identify the two comparison groups. Data to be obtained from each household at this stage consist of the number of children under 2 in the household, whether children under 2 were born in Santo Domingo, presence of smokers in the household, use of residence for certain jobs and the correct address for eligible households. Since less than half of the households are likely to have children under 2, and half of these will have at least one smoker, most household visits at this stage will be very brief. Given the limited amount of data to be collected at this state, it is estimated that the average visit will take an interviewer from 5-10 minutes. Since households to be surveyed at this stage are in the same neighborhood and adjacent to each other, the time it will take an interviewer to go from one household to another is estimated to be no more than 2 minutes. For this phase of the study, it is estimated that an interviewer can conduct, on the average, 30 interviews per day. (In the recent pilot survey, interviewers were able to conduct 20 interviews/day using a much longer questionnaire). The total number of households to be surveyed to identify required number of eligible children is estimated to be no more than 7800 (see 11.b.10). With an average of 150 households surveyed per day, the identification of the study population can be completed in 10 working weeks.

Four nurses will be hired to work on a full-time basis as field health workers. They will be trained and certified in interviewing mothers/care takers of children, in checking children for signs and symptoms of ARI and for measuring MUAC. They will conduct the follow up visits, where data on recent episodes of ARI, cooking activities and select control variables will be collected. Every day, each field health worker will be responsible for collecting data on 11 study subjects. As each of these workers will conduct follow up visits in just one neighborhood every day and the average duration of each of these visits will be no more than 30 minutes, it is estimated that each field health worker will

complete her daily tasks in about 6 hours. The extra time during the day may be used to conduct previous follow up visits that for one reason or another ended up being postponed. A fifth nurse will be trained to allow flexibility to replace any field health worker if needed.

The above time estimates for the follow up visits are based on prior experience. In the recent pilot survey of Santo Domingo that used a questionnaire similar to the one proposed for the follow up visits in this study, each interviewer was able to visit an average of 20 households/day. Worth noting is the fact that the population in Santo domingo is generally very cooperative with surveys. For example, in the recent survey where 1333 households with children under 5 years were visited there were no refusals.

Five people will be hired, trained and certified in handling the particle samplers and the NO_2. Each one of them will place an air sampler and an NO_2 passive sampler in 2 different households before the first cooking activity, will retrieve the sampler the same day after the last cooking activity and, at that time, will gather information on cooking activities during the day. Strict criteria regarding the placement of the air pump will be used in order to reduce observer bias. The PVC membrane filter cassettes which will be used in assessment of respirable particulate (RP) concentration are generally stable during shipment.[76] The azo dye forming reagent used for the NO_2 is subject to a loss of color during storage. The two field blanks submitted with each batch of ten samples will be used as reference samples in spectrophotometry following standard methods[77] to compensate for dye changes in transit. The NO_2 field blanks will be identified as references samples. Regular submission of blank and replicate samples (both NO_2 and RP) will be used to confirm quality control.

One industrial hygiene specialist will be hired to train and supervise the particle sampling. Another supervisor will be hired part time to help in overseeing the work of the data collectors. One laboratory assistant will be hired to carry out the filter weighing and spectro-photometry at Johns Hopkins.

II.b.8 Exposure Assessment

Cooking fuel reports

At each of the bi-weekly follow up visits, mothers will be interviewed regarding cooking activities and the child's activities during the previous day. Data to be collected on such activities will include amount of wood charcoal used, type of wood, type of food prepared, the amount of time that the stove was used, the room

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where the child spent his time during the cooking, and the child's activities at the time of the cooking. These data will be used to create an index of potential exposure that is time-dependent.

Reports on the type of cooking fuel will be used to classify subjects as exposed or not exposed. A child living in a household where wood charcoal is the only reported source of energy for cooking purposes will be considered as having potential charcoal smoke exposure. A child living in a household where propane gas or electricity is the only reported source of energy for cooking will be considered as having negligible potential charcoal smoke exposure. Households where wood charcoal and other types of fuel are used are rare and will not be included in the study population.

Since potential exposures can change qualitatively over time (i.e. a household could change its use of cooking fuel during the follow up period, from wood charcoal to gas for instance), and this change could vary between households where such a change occurs, the exposure classification system will include an element of follow up time.

Environmental Assessment

During the periods January-March and July-September an air sampler will be placed for three randomly selected days in every household. The sampler will be placed during the morning, before starting the cooking activities and will be retrieved the same day after the last cooking activity has ended (i.e. the sampling time would be about 12 hours). While retrieving the sampler the data collectors will gather information on cooking activities during that day. Sampling will not be done during the night because of logistic and privacy reasons. In addition, since there is no cooking during the night and respiratory rates are reduced while sleeping, the potential exposure to wood-charcoal smoke is likely to be minimal during this period.

1. Ventilation assessment

Residential air pollutant concentrations generally depend on the rate of pollutant generation (cooking appliance type, usage and fuel employed), and the effective ventilation of the residence by mechanical (fan assisted) or natural ventilation (open windows, air leaks, etc.).[78] Natural ventilation will be affected by wind speed and direction, by portal area (size and degree of window opening), and by construction characteristics (air tightness of the building envelope). The extent to which ventilation reduces indoor pollutant levels depends on the pollutant concentration in the outdoor (ambient) air, which may not be zero. Ventilation

effectiveness is usually expressed as air changes per hour (ACH), accommodating differences in house internal volume.

In relatively airtight North American residences, it is practical to quantify the effective air exchange rates of buildings by measuring the average concentration,[79-80] or concentration decay of a non-reactive tracer gas.[81] In North American residences during the winter when infiltration of outdoor air is intentionally minimized, indoor air exchange rates may range from 0.2 to 0.8 ACH and are associated with elevated indoor air pollutant concentrations.[82] We believe that the use of tracer gas techniques to assess infiltration in the typical residence in Santo Domingo would not be practical since air exchange rates are greater than in North American residences where the techniques have been tested.

A typical single-family residence in Santo Domingo measures about 10 ft. x 40 ft. and contains two or three rooms. The building materials include wood or concrete block walls, sheet metal or poured concrete roof, and unglazed windows on each wall. Mechanical ventilation systems are rare; natural ventilation by light prevailing (tropical) winds is assisted by the large open windows. Cooking is typically conducted over an unenclosed wood-charcoal fire on the floor (no chimney), or occasionally on propane or electric stoves. While cooking, a light haze is sometimes visible within the residence. Unlike a typical North American residence with a small pollutant source (gas stove) in a relatively airtight building, cooking in Santo Domingo typically involves a greater pollutant source within a less enclosed structure.

At the beginning and end of each sampling day, we will measure the air velocity (and direction) through windows and doors using a calibrated hand held anemometer (Kurz), as well as the outdoor wind speed and compass direction. We will measure the open area of windows, record the floor plan (including cooking location), and measure the compass direction of the long axis of the house. ACH will be taken as: (window air velocity) x (window area) / (room volume). To assess the average ventilation effectiveness during the day, we will compare the wind speed and direction measured at the residence with the records maintained at Santo Domingo airport. We will record the location of nearby outdoor bluff bodies or walls which might affect wind speed or velocity. We will classify ventilation for each room on the basis of ACH and the orientation of the room (upwind or downwind) to the cooking plume.

A highly simplified model of a typical Santo Domingo Residence is presented to illustrate the limitations of conventional (tracer gas) methods for quantitative measurement of residential ventilation (air changes/hour, ACH) with unvented combustion. In

an effort to classify the residences at the time of air sampling as well- or poor-ventilated, a series of relatively simple measurements to estimate ACH are proposed. Measurement of ACH will permit subsequent analysis of its role on RP concentration and ARI incidence. A sketch of the floorplan showing pollutant sources and exposure areas is standard practice in environmental monitoring and, in this study, can permit subsequent comparison of site (residence) wind speed and direction to that observed at The Americas airport (1) on the day sampled and (2) on average for the study period. Knowledge of site specific wind data and the collection of the cooking facility with respect to the rest of the house will permit classification of exposure as generally upwind or downwind of the cooking plume.

2. Respirable Particulate Concentration

We will measure respirable particulate (RP) concentration as a surrogate measure of wood charcoal smoke (WCS) concentration. Because indoor particles may be from different sources (e.g., WCS, road dust, animal dander), we propose to measure the concentration of particles in the size range of WCS and exclude others. Particles which result from combustion processes are typically less than 2 µm in size and are formed as hot vapors condense in the combustion plume.[83] Particles which result from mechanical processes (crushing, grinding, road dust) are typically larger than 5 µm in size.[83] An RP sampler consists of an air pump, a filter, and a cyclone preseparator. The air pump draws an air sample through the cyclone which removes particles larger than about 7 µm in size from the airstream.[84] Particles smaller than 7 µm in size penetrate beyond the cyclone and are collected on a filter whose weight gain is taken as the mass of RP in the volume of air sampled by the air pump. RP sampling is usually used to collect the fraction of inhaled aerosol which is capable of penetrating to the gas exchange region of the adult lung.[84] Although the adult and child lungs differ substantially in size, model studies,[85] predict that particle deposition in the lungs of a 22 month old child is not substantially different than in an adult. Hence, RP sampling in this study will measure exposure to both WCS and other particles which could penetrate to the lower respiratory tract. To the extent that other fine particulate pollutants (e.g., ETS) are collected by the RP sampler, this surrogate measure may overestimate WCS exposure. However, since other sources of fine particulate pollutants are expected to exist in both groups of households, any excess on their level could be imputed to WCS. A environmental questionnaire will be designed to identified other sources of RP. RP will be monitored for 8-12 hours during the day in the child's sleeping and living rooms using two portable constant-flow battery-powered air pump (Gillian HFS-513A sampling pump) each of which draws indoor air at 1.7 liters/min through a 37

mm PVC membrane filter (Gelman VM Metricell, 5 μm pore size) installed in a filter holder fitted with a cyclone preseparator (Gillian). The sampling pump flow rate will be checked before and after sampling using an NBS traceable flow standard (Minibuck calibrator). Two field blanks will be submitted with each batch of ten filter samples to monitor quality control. All sample filter media will carry barcode and numeric identifiers; samples and blanks will not be distinguished by marking. Standard methods of analysis will be used.[76]

The gravimetric analysis for respirable aerosol will be conducted at Johns Hopkins with a Cahn Model C31 electrobalance, which is capable of weighing to the nearest 0.1 micrograms. Balance calibration will be checked daily with a National Bureau of Standards (NBS) traceable calibration weight. Prior to weighing, filters will be exposed to a polonium-210 static neutralizer to reduce the net filter charge. The limit of detection for an 8 hour RP sample is lower than 10 $\mu g/m^3$ (less than 4% of the US National Ambient Air Quality Standard for Particulate Matter of 260 $\mu g/m^3$). The RP concentration in Santo Domingo's households should be well above the specified limit of detection.

3. NO2 Concentration

NO2 will be monitored for 12 hours during the day in the child's sleeping and living rooms using passive dosimeters (SKC Passive Bubbler) which contain an azo dye forming reagent which reacts with NO2 to form a color which can be analyzed by spectrophotometry (Bausch and Lomb Spec 20) following standard methods.[77] The passive dosimeters will be prepared and subsequently analyzed at Johns Hopkins. Two field blanks will be submitted with each batch of ten samples to monitor quality control. All sample media will carry barcode and numeric identifiers; samples and blanks will not be distinguished by marking. The limit of detection is expected to be lower than 0.01 ppm for an 8-hour sample.

11.b.9 Health Status Evaluation

During the first interview baseline data will be gathered on those who accept to participate in the study. During the biweekly health evaluations the health workers will record information on symptoms and signs of ARI on the day of the interview. The time window for data collection will be four days around the corresponding day and two more attempts will be made if for any reason the health evaluation can not be carried out when planned.

The data forms will be pilot tested on the mothers of children attending the Robert Reid Cabral Children Hospital. The training of nurses will also take place at this institution. The questionnaire will include questions such as:

In the past two weeks:

- Has your child had a runny nose?
- Has your child had fever?
- Has your child had an earache?
- Has your child had a cough?
- Has your child breathed faster than usual?
- Has your child had difficulty breathing? (show diagram of child with chest retractions)

The above questions are similar to those mothers are asked when they take their children to a health care provider for evaluation of an ARI or in epidemiologic studies of ARI. Such maternal reports of ARI signs and symptoms in their children are reliable provided such data relate to recent events. In this study, at each visit queries of mothers regarding possible ARI signs and symptoms in their children will be limited to the preceding two weeks. Given that signs and symptoms of an ARI may last from 2-7 days, the actual recall period for many ARI will be about a week or less; for many ARI there will be no need for recall as they will be symptomatic at the time of the visit. Nonetheless, an assessment of the reliability of the recall data will be made by determining the rate of ARI by the number of days since the last interview. This will not only indicate whether recall errors exist but also provide an estimate of the magnitude of such errors and ways to correct for possible underascertainment errors.

11.b.10 Sample Size

The following formula was used to calculate sample size:

$$Nc=(Z_{\alpha} + Z_{\beta})^2 / 2(\sin^{-1}\sqrt{P_c} - \sin^{-1}\sqrt{P_t})^2$$

where, Nc=sample size in each group;
P_c= estimated annual incidence of pneumonia per child/year in the non-exposed group.
P_t= RR x P_c; and
RR= estimated relative risk associated with exposure[85].

The following table shows the sample sizes for different relative risks (RR) and LRI incidence (P_c) power $(1-\beta)=.80$; $\alpha=0.05$ for a one-tail test; and n for each group.

Pc	Relative Risk		
	1.4	1.5	1.6
0.15	505	333	238
0.20	351	230	164
0.25	258	169*	119
0.30	197	128	90

(*) Selected sample size

A cohort of 169 exposed children and an equal number of non-exposed children will allow us to detect a 50% increase in the incidence of LRI with a power of 80% and a confidence level of 95%. Losses to follow-up and refusals are estimated to be less than 10%.[34,41] Therefore, 200 children in each group should provide an adequate margin for such losses and still insure sufficient power. Since 20.5% of the households in Santo Domingo have at least one child less than 2 years old,[41] 50% have at least one smoker and 25% of households use wood-charcoal for cooking purposes,[87] at most 7,800 households will have to be visited to obtain about 200 with "potential exposure" and a sample of 200 children without "potential exposure" matched to the exposed group on age and neighborhood. We expect to be able to enroll all children from only three or four neighborhoods.

As the two comparison groups will be matched on age and neighborhood, the number of variables for which adjustment may be necessary should be few. As the two groups will be rather similar in many respects, it is very unlikely that the power for the specified sample size will be significantly compromised in the multivariate analysis.

Regarding URI, the incidence is about 6 episodes per child-year,[34] many times that of LRI. Consequently, the study power will be sufficient to detect even smaller relative risks.

11.c Data Analysis

The analysis will begin with simple summary statistics to look at the comparability of both cohorts and to estimate and compare the incidence of LRI and URI between them. Frequency of LRI and URI will be expressed as incidence density with person-time experience as denominator.[88] Person-time experience will be allocated for each child up to the date when last observed. The time of duration of an ARI episode plus three days after its cessation will not be counted as person-time at risk for either LRI or URI regardless of the type of ARI episode.

In the preliminary analysis, incidence rates will be estimated based on the assumption that they follow a Poisson renewal process. Total number of cases will be divided by the amount of person-years in each group. Also, for URI the "rate of recurrence" defined as four or more episodes of URI during the study period will be estimated. For LRI time up to the first episode be used to estimate the rates. This latter approach may result in some loss of information for both types of outcome. In either case, the loss of information is not likely to be very important since repeated episodes of LRI in the same child are not very frequent and the number of children with four or more URI episodes is not likely to be very large.

The rate ratio or the relative risk will be used as a measure of effect. Adjustment for potential confounders will be initially done by direct standardization using the non-exposed group as reference category. This will be used for first episode of LRI as well as URI recurrence rate.

In addition, the proportional hazard model developed by Cox[89] will be used to evaluate the association between smoke exposure and time to the first LRI episode while controlling for confounding factors. This procedure will allow us to deal with variable lengths of observation among the two cohorts. An autoregressive term will be included in the model in order to evaluate the effect of previous ARI episodes.[90]

Nonparametric methods and simple linear regression will be used to compare the mean number of URI episodes among the different exposure groups.

Quantitative information on exposure will be used to categorize children by levels of exposure and to analyze dose-response relationships. Difference in the duration of LRI and URI episodes between exposure groups will be analyzed by multivariate regression techniques.

11.d Data Management

Data Collection and Storage

Office space will be secured at AUSD for data storage, management and preliminary analysis. At this facility, designated Data Management Center, data will be stored, entered onto magnetic media and checked for missing or erroneous data items. Data quality and confidentiality will be maintained. This Center will be directed by a half-time computer programmer. The computer programmer will be responsible for designing and supervising the information system.

Every child in the study will be assigned a unique identifier number which will be used in each form used to collect information on him: health evaluation forms and environmental evaluation forms. All data forms will be pre-coded and data collectors will be responsible for checking them before delivering them to the Data Management Center. The data will be entered into a Database System on an IBM PC/AT computer as soon as possible after collection. Double data entry and cross checking will be done to reduce the error rate as far as possible.

In order to keep information confidential only personnel directly responsible for the study will have access to the information. The file linking the identifying number and the name and address of the children will be available only to Dr. Bautista and the computer programmer. The study results will be available only in the form of averages.

Quality Assurance Procedures

- An operation manual defining the recruitment and the follow up process, the laboratory methods, the different study forms and questionnaires and the instructions for their use as well as the procedures for data handling will be elaborated at the beginning of the study. This manual will serve as a way of communication between the different investigators involved in the study and as a guide for the different activities in the study.

- Interviewers and environmental data collectors will be trained and certified at the beginning of the study. Retraining will be done at 6 months after the start of follow up. A hierarchical system of supervision aimed at detecting any departure from the protocol and the eventual need to retrain before the established date will be in effect from the start.

At the end of the training period the performance of each data collector will be evaluated.

- Data collectors will be carefully trained in recognizing ARI symptoms and signs present during the health evaluation visits and to accurately record ARI manifestations reported by the child's mother.

- The case definition will be compared with a sample of children attending the Robert Reid Cabral Children Hospital as an assessment of agreement.

- Each possible episode of ARI will be examined independently by two members of the research team using the case definition criteria and without knowledge of the exposure status. This will help to detect any inconsistencies in case ascertainment and in classification of cases on severity of the episode. In case of disagreement between two investigators, a third investigator will be asked to assess the case.

- Specific guidelines will be defined for the laboratory measurements. These guidelines will be aimed to avoid labelling errors and observer bias as well as to check on the validity and consistency of the laboratory measurements through the used of standard blanks (cassette filters and NO_2 diffusion tubes). Environmental measurements will be closely supervised by one of the co-principal investigators and the supervisor. The sampling pump flow rate will be checked before and after sampling using an NBS traceable flow standard (Minibuck calibrator). Two field blanks will be submitted with each batch of ten filter samples to monitor quality control. Filter weighing will be done without knowledge of the type of fuel use in the household where the sample come from. Filter weighing will be done twice for a subsample of 10% of all the samples and the microbalance will be calibrated daily (see 11.b.9).

- To prevent errors during data handling the study forms will be precoded, and the person responsible for filling the form will check it before returning it to the study center. Data entry will be done in duplicate and resulting files compared for consistency. Computer will be programmed to detect aberrant values during data entry and frequency distributions will be obtained frequently to check for inconsistencies.

- Supervisors will directly oversee the work of each data collector at least once a week.

- The project director will meet weekly with the supervisors in order to explore the development of unforseen problems during the field work and to make any adjustments to the data collection time table. He will also meet with the data collectors, supervisors and computer programmer once a month and whenever else needed. He will be responsible for bi-weekly progress reports to the research team, for keeping the research team abreast of any new problems, and for periodically meeting with members of the research team at AUSD, Santo Domingo, and at JHSHPH, Baltimore.

- Although the quality assurance procedures will be the responsibilities of the various members of the study team, a quality assurance officer will be in charge of overseeing the implementation of such procedures.

11.e LIMITATIONS

11.e.1 Selection Bias

A possible source of bias in any cohort study is losses to follow up, especially if they differ by study group. Nevertheless, we do not expect many losses to observation since the study population is not a highly mobile one and the households will be frequently visited. Since the follow up is for one year only, we do not expect a significant number of drop outs. In any event we do not foresee any reason to expect losses to be differential.

11.e.2 Information bias

- <u>Incomplete ascertainment</u>

Even though information on outcome will be obtained every two weeks, some degree of under ascertainment may occur due to poor recall. Poor recall may apply to mild cases of URI. Given that signs and symptoms of an URI may last from 2-7 days, the actual recall period for many URI will be about a week or less; for many URI there will be no need for recall as they will be symptomatic at the time of the visit. Nonetheless, an assessment of the reliability of the recall data will be made by determining the rate of URI by the number of days since the last interview. This will not only indicate whether recall errors exist but also provide an estimate of the magnitude of such errors and ways to correct for possible underascertainment errors.

Since cases of LRI are usually symptomatic and result in medical attention, it is unlikely that the child care taker will

forget them. Thus, under ascertainment of LRI episodes should be negligible.

- Misclassification of outcome

Among the ARI cases in the study, some of the mild cases of LRI may be misclassified as URI; similarly some of the more symptomatic cases of URI may be misclassified as LRI. To control for the possibility of this type of misclassification, analysis for each type of outcome will be stratified by severity.

- Misclassification of exposure

Particles are a good surrogate measure for level of charcoal-smoke exposure since they include many of the potential specific agents increasing ARI. However, particles may not be the ideal indicator of all possible agents, especially gases. This problem has no solution since it is practically impossible to measure all possible specific agents produced by charcoal-smoke. Some degree of error in the quantitative measurement of the exposure may lead to misclassification in the assignment of the dose level for each child. Such a misclassification should be non-differential. Nevertheless, it is reasonable to expect a very high correlation between particle concentration as measured in our study and actual values of particle concentration. Under these circumstances, the bias toward the null if any should be unimportant.[91] Since the main difference between the two groups of households regarding sources of air pollutants would be the fuel used for cooking, differences in the incidence of ARI could be attributed to the latter.

- Interviewer bias

Since the health workers may be aware of the child's exposure status, bias may occur while questioning about signs and symptoms of ARI. We intend to minimize this source of bias by carefully training the data collectors, by keeping them as blind as possible on information on the evaluation of the exposure, and by assigning them an equal number of exposed and non-exposed to be evaluated. In addition, the final assignment of case status will be done during the analysis by combination of symptoms and signs and every effort will be done to keep the interviewers unaware of the main hypothesis being tested. Laboratory procedures will be carried out without knowledge of the ARI experience in the households sampled.

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11.f Time Table

1/1/91	Earliest start possible
1/1/91 - 3/1/91	Forms and questionnaire development Personnel hiring Interviewers training
3/1/91 - 6/1/91	Sample frame construction Sample selection Particle Data collectors training Pilot testing of data forms Data management system development
6/1/91 - 9/1/92	Enrollment and Follow-up
9/1/92 - 3/1/93	Data analysis/presentation

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Addendum #1.

REPORTS OF STUDIES ON WOOD-SMOKE AND RISK OF ARI.

Author	Place	Date	Type	Pop.	ARI	Results
Ander-son	PNG	1978	Cohort (30wks	<15 yrs Exp=87 NExp=25	Symptoms	No diff.
Kossove	S.A.	1982	CCS	Infants Cases=132 Ncases=18 LRI	LRI	OR=4.8 (1.7-13.6)
Tuthill	U.S. (MA)	1984	Cohort Nonconc.	6-12 yrs Exp=259 Nexp=140	Excess illness	RR=1.1 (0.8-1.7)
Honicky	U.S. (MI)	1985	Cohort Nonconc.	1-7 yrs Exp=31 Nexp=31	Symptoms (*)	RR=4.0 (3.0-146.6)
Pandey	Nepal	1985	Survey	<5 yrs N=1085**	ARI by severity	+ Dose response

(*) Result for moderate symptoms.
(**) Exposure measured as time expended at the kitchen.
Numbers in parenthesis are 95% confidence limits.

Adolfo Correa Villaseñor
Charcoal-smoke and ARI

Addendum #2

PILOT STUDY FINDINGS

1. Study Population

Santo Domingo, the capital of the Dominican Republic, is a city with a population of approximately 1.5 million. Santo domingo is an urban area with few industries, most of which are located outside the city. The main source of outdoor pollution within the city is considered to be combustion of fossil fuel by automobiles.

Santo Domingo residents live in neighborhoods defined by socioeconomic status. There are about 300,000 households distributed among 100 neighborhoods. These neighborhoods are a melting pot of different nationalities and demarcation of the neighborhoods in terms of race or ethnicity is impossible.

Four neighborhoods were selected for this pilot survey. The objective of the selection was to obtain neighborhoods likely to have a high use of wood charcoal for cooking purposes. Four low and middle income neighborhoods were selected for the survey. Data were collected on a total of 1333 households with children less than five years of age by systematic sampling of households in these four neighborhoods.

2. Household Characteristics

The selected neighborhoods, as most of the Santo Domingo population, are located in areas where outdoor air pollution appears to be of no significant magnitude. Most of Santo Domingo's houses are built out of cement, wood and zinc sheets. Thirty nine percent have concrete walls and zinc ceiling, 31% have concrete walls and ceiling and 23% have wood walls and zinc ceiling. The typical household has from two to 5 rooms (median=4). The rooms in a typical house include two bedrooms, a kitchen and a living room.

The median number of people per household is 6 (mid-fifty=4,7). The mean sleeping density (crowding) is 3.6 people per bedroom, 3.4 for households where propane gas is used for cooking and 4.3 for households using charcoal smoke ($P<.001$).

In 75% of the households, one room is used exclusively as a kitchen. However, in 20% percent of the household units, cooking activities are carried out in a bedroom or the living room. Cooking is carried out three times a day in 79% of the households while only 15% do this activity twice a day and the rest only once. Whereas in 82% of households with gas stove cooking is done three times a day, this only happens in 68% of households with charcoal

stoves. The mean number of hours cooking per day is 3.42 for households using gas-stove and 3.61 for those using wood charcoal (0.01).

Thirty four percent of the children (459) were less than 2 years of age. In 441 of these children exposure status was ascertained and 23% (102) were classified as exposed to charcoal smoke.

3. ARI Incidence

ARI episodes during the week previous to the survey were identified by interviewing the mother of each child or the child care taker. The definition of an ARI episode was decided previous to data collection. An episode of ARI was defined as anyone of the following:

a. Any child whose mother reported as having been diagnosed by a physician as having a respiratory infection during the previous week;

b. Any child who during the previous week has had cough and fever for more than two consecutive days;

c. Any child with sore throat for more than two days and fever for at least one day;

d. Any child with an ear discharge or earache;

e. Rapid breathing for more than two days together with fever for at least one day.

f. Shortness of breath for more than two days plus fever for at least one day (asthma cases were excluded on the basis of a physician diagnosis).

Using the stated criteria for ARI diagnosis we detected 92 cases of ARI. The incidence rate was 21 per 100 children-weeks which is equivalent to 10.9 episodes per child year (assuming that the distribution of ARI episodes is homogeneous throughout the year). The age specific rates are shown in Table 2.1.

Table 2.1

ARI rates per 100 children-weeks by age, Santo Domingo, 1990.

Age (months)	N	Cases	Rate (95% C.I)
0 - 6	114	22	20 (16, 22)
7 - 12	127	33	26 (23, 29)
13- 18	108	22	20 (17, 23)
19- 24	92	15	16 (14, 19)
Total	441	92	21 (19, 22)

Three cases of LRI were reported by child care takers as being diagnosed by a physician. This figure corresponds to a LRI incidence of 27 cases per 100 children-year, although the small number of cases makes it very unstable. Cherian has reported that the proportion of LRI among ARI episodes in children from underdeveloped countries is 3% in children 1-5 years old and 1.5% in children less than one.[35] Using these proportion we have estimated that the incidence of LRI infection in the survey population is 24.5 cases per children-year. Although and indirect estimate this figure is consistent with the LRI incidence rate based on physician reported cases and also with reports from other populations. For instance, in a review article Graham[14] has estimated that in developed countries the LRI incidence is 25 per 100 children year in infants and 18 per 100 children year in preschool children, while in a active surveillance study in infants, Wright at al.[1] have found an incidence of 32.9 cases per 100 children-year. Since risks factors for LRI, like malnutrition, low level of maternal education and crowding are more frequent in populations from less developed countries than they are in developed countries, the LRI incidence in the former should be higher than in developed countries.

4. Agreement of the Survey ARI Case Definition with Medical Diagnosis

[1] Wright, AL at al.: The Tucson children's respiratory study. II. Lower respiratory tract illness in the first year of life. Am J Epidemiol 1989; 129:1232-46.

Eighty percent of the children with ARI during the previous week (77 cases), were taken to a physician. This allowed us to check our diagnostic criteria. We compared the performance of our diagnostic criteria to the diagnosis reported by the mother among children who attended to a clinic (Table 2.2).

Table 2.2

			Physician Diagnosis ARI		
			+	-	Total
Interview	ARI	+	72	3	75
		-	2	15	92
		Total	74	18	92*

* In four cases the mother did not remember the diagnosis or the physician did not tell her.

The percent agreement was 94.6%, with agreement beyond chance being 82% (kappa statistic). Although the pilot study was not specifically designed to evaluate the validity of the case definition, these figures provide some assurance about the reliability of the case definition.

5. <u>Exposure effect</u>

Children exposed to charcoal smoke were 1.2 times more likely to have had an episode of ARI during the previous week (95% confidence limits [CL]: 0.7, 2,2). Using a logistic model we adjusted by age, sex, number of children less than 5 in the household, mid upper arm circumference and maternal education. None of these variables resulted in significant changes in the crude odds ratio.

The estimated odds ratio measures the effect of charcoal smoke on URI since very few LRI cases were detected. Since charcoal smoke is likely to mediate its effects through respiratory particles which are deposited in the lower air way regions, it its reasonable to expect the effect of charcoal-smoke to be greater in LRI incidence than in URI incidence. Therefore, for the sample size and power calculations we have estimated the relative risk to be around 1.5. This relative risk is below the relative risk associated with indirect exposure to tobacco smoke (RR=2.0), a

known risk factor whose composition is similar to that of charcoal smoke.

6. Some Potential Confounding Factors

Nutritional status

We were able to measure mid upper arm circumference (MUAC) in a subset of 292 non exposed and 88 exposed children. The MUAC was 15.17 cm. and 14.76 cm. for non exposed and exposed children, respectively. Once adjusted by age and sex the mean difference in MUAC between non-exposed and exposed children was 0.4 cm (95% CI: 0.0, 0.8).

A MUAC less than 13.5 cm in children 1-5 years old[71], and less than 12.5 in infants[72] is an indicator of malnutrition. Using this classification we found a prevalence of malnutrition (severe + moderate) of 10% among 174 one year old children (95% CI: 8%, 11%) and 8% among infants (95% CI: 7%, 9%). Exposed children were in average 1.1 times more likely to be undernourished than non-exposed children (95% CI: 1.0, 1.2). However, children with low MUAC were similar to those with normal MUAC regarding the incidence of ARI(RR=1.0; 95% CI: 1.0, 1.1). Once adjusted for nutritional status the RR associated with exposure to charcoal-smoke was reduced from 1.2 to 1.1 (95% CI: 0.7, 1.8). From these data, nutritional status does not appear to be a strong confounder of the association between exposure to charcoal-smoke and URI incidence.

Birth weight

Birth weight data were obtained from the child's mother. For this group of children, neither age nor sex were significant predictors of the reported birth-weight. The mother education was associated with the reported birth weights. On average, each unit decrease in the educational level (see table 2.4) corresponded to an increase of 1.7 times (95% CI: 1.1, 2.5) in the frequency of low birth weight (<2500 gr.). This is what was expected. However, exposure status was not significantly associated with low birth weight (OR=0.55; 95% CI: 0.2, 1.3). Birth weight did not act as a confounder for the association between ARI an exposure to charcoal smoke.

Socio-economic status

It is reasonable to assume that the type of fuel used for cooking would be associated with socioeconomic status. Socio-economic status is usually measured by three indicators: level of education, income and occupation. We have used education and family income as surrogate for socio-economic status.

Our data show that families using propane gas for cooking have a higher monthly average income than families using wood-charcoal Table 2.3).

Table 2.3

Distribution of population by average monthly income and type of fuel used for cooking, Santo Domingo, 1990

Average Monthly Income (RD$)*	Type of fuel used for cooking	
	Propane Gas	Wood-Charcoal
< 500	44 (4.7%)	31 (14.2%)
500 -	231 (24.7%)	84 (38.5%)
1000 -	211 (22.5%)	65 (29.8%)
1500 -	170 (18.2%)	24 (11.0%)
2000 -	139 (14.9%)	10 (4.6%)
2500 +	141 (15.1%)	4 (1.8%)
Total	936 (81.1%)	219 (18.9%)

* Per capita

Although income is clearly higher in families cooking with propane gas, the high degree of overlap of both distributions suggest that adjustment could be successfully carried out by stratification and regression analysis.

A similar situation is observed with education (Table 2.4). Even though mothers of non exposed children have higher levels of education, there is a great amount of overlap of the distributions of years of education and adjustment during the analysis could be attainable.

Table 2.4

Mother's educational level by type of fuel used for cooking, Santo Domingo, 1990

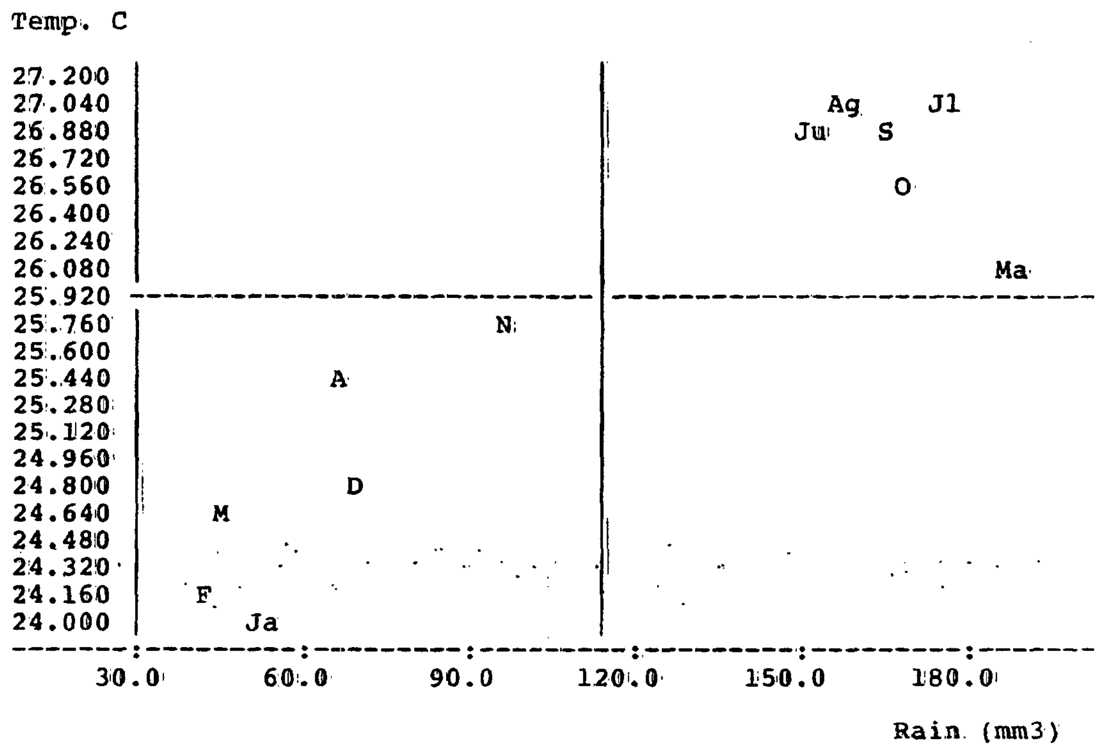
Education (years)*	Type of fuel Used for cooking Propane Gas	Wood-Charcoal
0	11 (3%)	12 (12%)
1-6	83 (25%)	25 (25%)
7-12	185 (55%)	55 (55%)
13 +	58 (17%)	9 (9%)
Total	337 (75%)	101 (25%)

* This levels correspond to the current organization of the school system in the Dominican Republic.

Confounding by race/ethnicity in this population is not a problem in this population. Santo Domingo has historically been a melting pot of different nationalities and distinction of individuals or groups by race is impossible.

Addendum #3

Average temperature by rain during the different months of the year (1931-1980)



Source: Oficina Nacional de Estadisticas: República Dominicana en Cifras. Vol. XIV, 1987.

Addendum #4

SENSITIVITY AND SPECIFICITY OF EITHER RAPID BREATHING AND CHEST RETRACTION EVALUATED BY DIRECT OBSERVATION OR BY MOTHER INTERVIEW IN DETECTING LRI AMONG CHILDREN WITH ARI

	OBSERVATION*		HISTORY**	
AGE	Sens.	Spec.	Sens.	Spec.
0-11 mo.	92% (53)¶	94% (902)	93% (142)	87% (151)
12-23 mo.	95% (42)	96% (1138)	89% (54)	90% (142)
24-35 mo.	90% (30)	98% (910)	94% (18)	92% (59)
>35 mo.	100% (29)	98% (1258)	67% (36)	93% (80)

* Campbell at al., *Lancet*, Sept. 24, 1988
** Cherian at al., *Lancet*, July 16, 1988
¶ Number of children with ARI

12. AVAILABLE FACILITIES AND RESOURCES

The Johns Hopkins University School of Hygiene and Public Health provides opportunities for education, research and service in the diverse fields of public health, including the primary disciplines of public health; basic and applied research; social policy; planning, management and evaluation of the delivery of health services; and in the environmental health sciences. The school also has cooperative relationships with external institutions and agencies at the local, national and international levels, including academic, governmental, and service organizations, all of which enhance the School's activities.

The Department of Epidemiology of the Johns Hopkins School of Hygiene and Public Health is the oldest academic Department of Epidemiology in the world and today ranks as one of the largest and most active departments anywhere. Faculty include physicians and non physicians with expertise not only in epidemiology but also in a wide variety of areas including clinical medicine, genetics, biostatistics, veterinary medicine, nursing, immunology, and nutrition.

Departmental interests focus not only on the etiology of disease and the relative contributions of genetic and environmental factors to the pathogenesis of disease, but also on the evaluation of health services and of new modalities of prevention and therapy.

The Department of Epidemiology has an extensive program of research with a major but not exclusive emphasis on cancer epidemiology and environmental epidemiology. Close bridging of the epidemiologic studies, both with clinical medicine and with laboratory science, is the basic approach which the Department pursues. In addition, there is a strong emphasis on the policy implications of epidemiologic data and on how such data can be translated into effective preventive efforts. Close relationships with the many other departments in the School greatly enhance the breadth and depth of the research conducted.

The department faculty is heavily involved in service activities including consultations both inside and outside the University. Members of the faculty serve on many national committees and study sections both in government and private industry.

Available facilities include: Three IBM 4341 at Informations Systems Department (ISD) at JHH. IBM 4341 at the University Computing Center and at the School of Hygiene and Public Health Academic Data Processing Center. All systems have extensive statistical and mathematical packages, some of which are: SAS,

SPSS, BMD, GLIM, Minitab and IMSL. All major programming languages are supported with heavy independence in our department on PL/1. Fortran and Basic. A large library of programs specific to the needs of epidemiological research has been developed and documented by staff within the department for data entry, crosstabs, linear and logistic regression and other epidemiological analysis.

All investigators at the School of Hygiene have adequate office space. It will be necessary to furnish an office for Dr. Bautista and the data manager in Santo Domingo.

13. BUDGET

13.a Personnel

Adolfo Correa Villaseñor, M.D., Ph.D., will be the principal investigator and responsible for all phases in the conduct of the study. His current research work is in occupational and environmental epidemiology and retrospective exposure assessment in epidemiologic studies. He will be responsible for all decisions regarding modifications of the study design, for monitoring progress reports and oral reports and for preparation of the final report.

Genevieve M. Matanoski, M.D., Dr.Ph.H., is a co-principal investigator with primary expertise in the field of occupational and environmental health epidemiology. She will assist Dr. Correa in various phases of project, including design, conduct, analysis and report preparation.

Leonelo Bautista, M.D, M.P.H., will serve as project director. He will be responsible for drafting and hiring personnel, for coordinating the research activities and training and supervising the data collectors and the supervisor of data collectors. Also, he will work with the principal investigator in all phases of this project, including dealing with design issues, supervision of the data management process, analysis and report writing. He is a member of the faculty at the Universidad Autonoma de Santo Domingo and will serve as liaison between this institution and the JHUSHPH.

Stephen Bowes, Ph.D., industrial hygienist, will serve as co-investigator. He will train and periodically audit performance of air sampling field team, oversee laboratory procedures and air sampling data analysis.

Victor Cairo, computer programmer, will be the Data Management Center Director. He will design the information system, will

perform and supervise data entry and will process the data files in order to facilitate data analysis.

K. Thomas, laboratory technician, will prepare particulate and NO2 monitors, track field samples, analyze samples returned from field, and assist in air sampling data analysis.

Quality assurance officer, to be hired, will be responsible for overseeing the implementation of the quality assurance plan and for conducting periodic audits to ascertain compliance with the plan.

Data Collectors. Four nurses will be hired as data collectors. They will obtain data on ARI symptoms and signs and will handle the air sampling devices. Five people will be hired to carry out the RP and NO_2 sampling. At the start of the study 5 data collectors will be hired for a two month period to gather the information for construction of the sampling frame.

Supervisor. Two supervisors will be hired: one, with experience in aerosol sampling, will overlook the RP and NO_2 measurements; the other one will oversee the work of the data collectors and will check the completeness and accuracy of the completed data collection forms.

Secretary. A full time secretary will be hired to support the investigators and the computer programmer in the carrying out of the daily administrative tasks, in scheduling meetings, and the preparation of reports.

13.b Supplies and Expenses

SKC passive bubblers, diffusion disks and other air sampling supplies will be used for NO2 and RP air concentration measurements.

The stationery will be used mainly to print the data forms needed for the study as well as for customary office work. An office for Dr. Bautista and the Data Manager will be furnished at AUSD in Santo Domingo.

A software package, DBASE IV, will be used for data storage and handling.

A digital thermometer will be handed to each child's mother participating in the study. An extra 34 thermometers will be reserved in case of need (10% of total sample).

Adolfo Correa Villaseñor
Charcoal-smoke and ARI

MUAC measuring tapes are required for the nutritional status evaluation.

Every week a set of filters will be shipped to JHUSHPH in order to carry out the laboratory analysis. Telephone and other communication costs will amount to U.S.$120.00 per year.

We are requesting $420 for publication costs.

13.c Travel and Expenses

Early in the study Dr. Correa will make one 5-day visit to Santo Domingo to oversee the initial implementation of the project, monitor initial progress, discuss design issues with the research team and make necessary modifications.

Dr. Bowes will make two 3 days visits to Santo Domingo in order to supervise the aerosol and NO_2 measurements.

Dr. Matanoski may need to travel to Santo Domingo during the early phase of the study to review progress and design problems that may arise.

At month 9 of the first year of the study, Dr. Bautista will travel to Baltimore, MD, to review and discuss progress of the project with the research team and to prepare the first progress report. Dr. Bautista will make another trip to Baltimore, MD, towards month 18 of the study to work on data analysis and writing the final report.

Expenses have been estimated based on U.S.$60.00 per day in Santo Domingo and U.S.$70.00 per day in U.S.

13.d Equipment

Five Kurz hot wire anemometers are requested for residential ventilation measurement. Four will be in constant use with the fifth available as a spare during repair or recalibration of other instruments. Ten sampling pumps and eight cyclones are requested for respirable particulate measurement. Eight pumps will be used routinely, with two as spares. Two Minibuck calibrators are requested for pump calibration. All equipment will be dedicated to this study. The air sampling instruments (pumps, cyclones, calibrators) of Johns Hopkins University are not available for a one-year deployment outside the U.S.

Computer equipment:

A PC/AT personal computer and computer devices will be used at the Data Management Center for data entry and data auditing. Similar use will be given to the data management software.

Salaries and fringe benefits for employees on-site in the Dominican Republic are in-country costs. Salaries in the Dominican Republic are significantly lower than those in the U.S. The minimum monthly salary is around U.S.$60. A graduate nurse makes from U.S.$150 to U.S.$200 a month. Full time data collectors are usually paid at U.S.$200-250 per month. Fringe benefits for

personnel in the Dominican Republic have been calculated at a 1.2% yearly rate. Fringe benefits for Dr. L. Bautista are based on the Johns Hopkins University's post-doctoral rate of 7.8% in both years. Those for other Hopkins' personnel have been calculated at .258 in the first year and .268 in the second.

14. BIOGRAPHICAL SKETCH

Adolfo Correa-Villaseñor, M.D.

REDACTED

Current Position

1987-90 Assistant Professor, Epidemiology, Johns Hopkins School of Hygiene and Public Health

Education

REDACTED

B.S. San Diego State University
M.S. University of California at San Diego
M.D. University of California at San Diego
M.P.H. Johns Hopkins School of Hygiene and Public Health
Ph.D. Johns Hopkins School of Hygiene and Public Health

Previous Positions

REDACTED

Research Assistant, Department of Chemistry, San Diego State University, San Diego, CA
Research Assistant, Department of Chemistry (1969), School of Medicine (1973), University of California San Diego, La Jolla, CA
Intern, San Francisco General Hospital, San Francisco, CA
Junior, Senior and Chief Resident, Pediatrics, University of California, San Francisco, CA
Epidemiologist, Epidemic Intelligence Service, Centers for Disease Control, USPHS, Atlanta, GA

REDACTED

Resident, General Preventive Medicine, Johns Hopkins School of Hygiene and Public Health, Baltimore, MD
Research Coordinator, Department of Epidemiology, Johns Hopkins School of Hygiene and Public Health, Baltimore, MD

Other Current Appointments

1989-90 Pediatrics, Johns Hopkins School of Medicine, Baltimore, MD
1990- Department of Epidemiology and Preventive Medicine, School of Medicine, University of Maryland, Baltimore, MD

Honors and Awards

REDACTED
Member, Phi Eta Sigma Honorary Society
National Science Foundation Traineeship, San Diego State University
University of California Regents Award, University of California at San Diego
Training Fellowship in Epidemiology, Johns Hopkins School of Hygiene and Public Health

Publications

Vold R, Correa A: NMR Measurements of proton exchange in aqueous thiourea. *J Phys Chem* 1970; 74:2674-2680

Correa A: Cardiopulmonary resuscitation appendix. In: Quick Reference to Pediatric Emergencies. Pascoe D And Grossman M (Eds). Lippincott, 1978, pp. 458-460

Bachrach L, Correa a, Levin R, Grossman M: Iron poisoning: complications of hypertonic phosphate lavage therapy. *J Pediatr* 1979; 94:147-149

Graham D, Correa-Villaseñor A, Anderson R, Volman J, Baine W: Epidemic Neonatal gentamicin-methicillin-resistant staphylococcal aureus infection associated with nonspecific use of topical gentamicin. *J Pediatr* 1980; 97:972-978

Halpin TJ, Holtzhauer FJ, Campbell RJ, Hall LJ, Correa-Villaseñor A, Lanese R, Rice J and Hurwitz ES: *Reye's Syndrome and Medication Use*. JAMA 1982; 248:687-691.

Correa A: Reye's Syndrome. In: A Continuing Education Course in Preventive Medicine. (audiovisual) Vol. 1, Program 5, Presentation 2. The Johns Hopkins University, School of Hygiene and Public Health, 1982.

Correa-Villaseñor A, Loffredo C, Ferencz C and Wilson PD: *Lead and Solvent Exposure During Pregnancy: Possible Risk of Cardiovascular Malformations*. Teratology 1990; 41:545.

Correa-Villaseñor A, Loffredo C, Ferencz C and Wilson PD: *Heterogeneity of Etiology and Exposure, Nondifferential Misclassification and Bias in the Study of Birth Defects*. Am J Epidemiol 1990; 132:796.

Correa-Villaseñor A, Boughman JA, Neill CA and Ferencz C: *Total Anomalous Pulmonary Venous Return: Familial and Environmental Factors*. To appear in Teratology (1991)

Correa-Villaseñor A, McCarter R, Downing J and Ferencz C: *White-Black Differences in Cardiovascular Malformations in Infancy and Socioeconomic Factors*. To appear in Am J Epidemiol (1991)

Stewart WF and Correa-Villaseñor A: *False Positive Exposure Errors in Case-Control Studies with Low Exposure Prevalence: Effects, Sources and Remedies*. In Proceedings from an International Workshop on Retrospective Exposure Assessment for Occupational Epidemiologic Studies. To appear in Applied Occ and Env Hyg (1991)

FF PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants listed on page 2. Begin with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	POSITION TITLE	BIRTHDATE (Mo. Da. Yr.)
Genevieve M. Matanoski	Professor	REDACTED

EDUCATION (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Radcliffe College, Cambridge, MA	A.B.	REDACTED	Chemistry
Johns Hopkins School of Medicine, Baltimore, MD	M.D.		Medicine
Johns Hopkins School of Hygiene and Public Health, Baltimore, MD	M.P.H.		Epidemiology
	Dr.P.H.		Epidemiology

RESEARCH AND PROFESSIONAL EXPERIENCE. Concluding with present position, list, in chronological order, previous employment, experience and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES

Professional Experience:

REDACTED

Pediatrics, Johns Hopkins Hospital, Baltimore, MD
Research Assistant, Epidemiology, Johns Hopkins School of Hygiene and Public Health, Baltimore, MD
Coordinator and Evaluator, Regional Medical Program, Johns Hopkins School of Hygiene and Public Health, Baltimore, MD

REDACTED

Instructor (1959), Assistant Professor (1964), Associate Professor (1969), Professor (1976), Epidemiology, Johns Hopkins School of Hygiene and Public Health, Baltimore, MD
Faculty, Preventive Medicine, University of Maryland, Baltimore, MD

Honors:

Training Fellowship in Public Health, Johns Hopkins School of Hygiene and Public Health, Baltimore, MD REDACTED
Certified Specialist in General Preventive Medicine, American Board of Preventive Medicine, REDACTED
Fellow of the American College of Preventive Medicine, REDACTED
Member, Delta Omega Honorary Society,
Member, American Epidemiological Society REDACTED

Federal Committees:

Consultant, Residency Advisory Committee of the Army Environmental Hygiene Agency, 1978-present
Member, EPA Scientific Review Committee for Health Research and Grants Review
Member, Board of Scientific Counselors, Division of Biometry and Risk Assessment, NIEHS, 1987-1991
Member, General and Plastic Surgery Devices Panel, FDA, 1988-1992
Member, Radiation Advisory Committee, EPA Science Advisory Board, 1990-1992
Member, VA Advisory Committee on Health Related Effects of Herbicides, 1989-1990

Publications:

Matanoski GM, Fishbein L, Redmond C, Rosekranz H, Wallace L: Contribution of Organic Particulates to Respiratory Cancer. Environment Health Perspect 70:37-49, 1986

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*Number pages consecutively at the bottom throughout the application. Do not use suffixes such as 5a, 5b.

OTHER SUPPORT

(Use continuation pages if necessary)

FOLLOW INSTRUCTIONS CAREFULLY. Incomplete, inaccurate, or ambiguous information about OTHER SUPPORT could lead to delays in the review of the application. If there are changes subsequent to submission, notify the executive secretary of the initial review group.

For each of the key personnel named on page 2, list, in three separate groups: (1) *all* currently active support; (2) *all* applications and proposals pending review or funding; and (3) applications and proposals planned or being prepared for submission. Include *all* Federal, non-Federal and institutional research, training, and other grant, contract, and fellowship support at the applicant organization and elsewhere. If part of a larger project, identify the principal investigator/program director and provide the data for both the parent project and the subproject. If none, state "none."

For each item give. (a) the source of support, identifying number and title; (b) percentage of appointment on the project; (c) dates of entire project period; (d) annual direct costs; (e) a brief description of the project; (f) whether the item overlaps, duplicates, or is being replaced or supplemented by the present application; delineate and justify the nature and extent of any scientific and/or budgetary overlaps or boundaries; and (g) any modifications that will be made should the present application be funded.

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR:

(1) CURRENTLY ACTIVE SUPPORT: (a)

Genevieve M. Matanoski, M.D., Dr.P.H.

Source of Support:	Establishing a Workplace
Project Title:	Health Profile System for the Pulp and Paper Industry
Principal Investigator:	Dr. Genevieve M. Matanoski
Percent of Effort:	30%
Project Period:	9/15/90-8/31/97
Annual Direct Cost:	$689,566 for 12 months
Description:	Determine health risks for workers in the paper industry.

Source of Support:	NIEHS
Identification Number:	5P30ES03819-04
Project Title:	EHS Center Grant - Core Unit I
Principal Investigator:	Dr. Genevieve M. Matanoski
Effort:	10%
Project Period:	09/01/87-08/31/91
Annual Direct Costs:	$43,775 for 12 months
Description:	Cancer Core Allocation

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Genevieve M. Matanoski, M.D., Dr.P.H.

(1) CURRENTLY ACTIVE SUPPORT:
(continued)

Source of Support:	NIOSH
Identification Number:	R01 0H02730
Project Title:	Case Control Study of Cancer in Synthetic Rubber Workers
Principal Investigator:	Dr. Genevieve M. Matanoski
Effort:	15%
Project Period:	06/01/90 - 05/31/92
Annual Direct Costs:	$229,255 for 12 months
Description:	To examine the risk of mortality from cancers and sarcomas from occupational exposure to butadiene and styrene and to determine if a dose response exists.

Source of Support:	Electric Power Research Institute
Identification Number:	RP 2798-01
Project Title:	A Study of Telephone Linemen to Determine Leukemia Risks from Electromagnetic Fields
Principal Investigator:	Dr. Genevieve M. Matanoski
Percent of Effort:	20%
Project Period:	06/15/90 - 02/28/91
Annual Direct Cost:	$126,958
Description:	Study to determine whether the exposure to electromagnetic fields increases leukemia risk in telephone linemen.

Source of Support:	EPA
Identification Number:	CR-817613-01-0
Project Title:	Risks Associated with Styrene in Synthetic Rubber Manufacture
Principal Investigator:	Dr. Genevieve M. Matanoski
Effort:	10%
Project Period:	10/01/90 - 09/30/91
Annual Direct Cost:	$33,634 for 12 months
Description:	To develop exposure levels of styrene as well as butadiene for each job in the industry by monitoring employees.

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Genevieve M. Matanoski, M.D., Dr.P.H.

(2) PENDING SUPPORT:

Source of Support:	EPA
Project Title:	Center for Environmental Epidemiology
Principal Investigator:	Dr. Genevieve M. Matanoski
Effort:	50%
Project Period:	04/01/91 - 03/31/94
Annual Direct Cost:	$896,053
Description:	Center to coordinate multi-disciplinary activity in the area of environmental risks in human populations.

Note: If all pending grants are funded, appropriate redistribution of salary and work will be made where necessary.

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Adolfo Correa Villaseñor
Charcoal-smoke and ARI

NAME	TITLE	BIRTHDATE
Stephen M. Bowes, III	Assistant Professor	REDACTED

INSTITUTION AND LOCATION FIELD OF STUDY	DEGREE	YEAR
U.S. Merchant Marine Acad., Kings Pt., NY Mechanical Engr.	B.S.	REDACTED
The Johns Hopkins Univ., Balto., MD Env. Hlth. Sci.	MHS	REDACTED
The Johns Hopkins Univ., Balto., MD Env. Hlth. Sci.	Ph.D.	

PROFESSIONAL EXPERIENCE:

REDACTED Assistant Professor, The Johns Hopkins University, School of Hygiene and Public Health, Division of Environmental Health Engineering, Department of Environmental Health Sciences

REDACTED Instructor, The Johns Hopkins University, School of Hygiene and Public Health, Division of Environmental Health Engineering, Department of Environmental Health Sciences

REDACTED Research Associate, The Johns Hopkins University, School of Hygiene and Public Health, Division of Environmental Health Engineering, Department of Environmental Health Sciences.

FELLOWSHIPS:

National Institute for Occupational Safety and Health Traineeship, REDACTED

Appointed to the U.S. Merchant Marine Academy by Congressman Charles E. Bennett of Jacksonville, Florida, REDACTED

BOARD CERTIFICATION:

Certified Industrial Hygienist (Comprehensive Practice), American Board of Industrial Hygiene.

PUBLICATIONS:

Bowes, S., R. Frank and D. Swift: The Head Dome: A Simplified Method for Human Exposures to Inhaled Air Pollutants. Am. Ind. Hyg. Assoc. J.: 51:257-260, 1990.

Bowes, S. and M. Corn: Noise Exposure Reduction Aboard an Oceangoing Hopper Dredge, Am. Ind. Hyg. Assoc. J.: In Press 1990.

Bowes, S., B. Laube, J. Links and R. Frank: Regional Deposition of Inhaled Fog Droplets: Preliminary Observations. Environ. Hlth. Perspect: (79) 151-157, 1989.

Bowes, S. and D. Swift: Deposition of Inhaled Particles in the Oral Airway During Oronasal Breathing. Aerosol Sci. and Technol.: 11:157-167, 1989.

Hemenway, D.R., G.J. Jakab, T.H. Risby, S.M. Bowes and R. Hmieleski: A Nose-Only Inhalation Exposure System Using a Fluidized Bed Generation System for the Generation of Co-Exposures to Carbon Black and Formaldehyde. Inhalation Toxicology, In Press, 1989.

Bowes, S.: Dilution Ventilation Modeling, Proceedings of the 1987 ASSE Professional Development Conference, Baltimore, MD, June, 1987.

Bowes, S. and D. Swift: Aerosol Deposition in the Human Oral Passage During Natural Oronasal Breathing. In Aerosols, Formation and Reactivity, Proceedings of the Second International Aerosol Conference, Berlin, September, 1986. Pergamon Press, 197-199, 1986.

PRESENTATIONS:

Laube B, S. Bowes, J. Links, K. Thomas and R. Frank: "The Effect of Acidified Fog on Short-term Mucociliary Clearance in Normal Subjects". Accepted for presentation at the 1990 World Conference on Lung Health.

Weinmann, G., S. Bowes and R. Frank. "Predicting Individual Susceptibility to Ozone Exposure". Accepted for presentation at the 1990 World Conference on Lung Health.

Frank, R., S. Bowes, B. Laube and J. Links: "Regional Deposition of Inhaled Fog Droplets: Preliminary Observations", presented at the International Symposium on Health Effects of Acid Aerosols, Research Triangle Park, NC, October, 1987.

Bowes, S., D. Swift and R. Frank: "The Head Dome: A Simplified Method for the Controlled Exposure of Human Subjects to Air Pollutants", presented at the 1987 Annual Meeting of the American Association for Aerosol research, Seattle, WA, September, 1987.

Bowes, S., H. Van Dusen, and D. Swift: "Design of a Modified Sinclair-LaMer Generator Producing Labelled Monodisperse Aerosols of Diameter Up to 20 Micrometers", presented at the Annual Meeting of the American Association for Aerosol Research, Albuquerque, NM, November, 1985.

Bowes, S. and D. Swift: "Oral Deposition of Monodisperse Aerosols in Humans During Oronasal Breathing", presented at the Sixth International Symposium on Inhaled Particles, Cambridge, England, September, 1985.

Adolfo Correa Villaseñor
Charcoal-smoke and ARI

Leonelo E. Bautista, M.D.

REDACTED

Current Position

REDACTED Dr.P.H. candidate, Department of Epidemiology, Johns Hopkins School of Hygiene and Public Health.

Education

- Autonomous University of Santo Domingo REDACTED

  Doctor of Medicine (MD).

- Autonomous University of Santo Domingo Public Health Department. REDACTED

  Master in Public Health.

Professional experience

REDACTED Epidemiologist, Hospital Infantil Robert Reid Cabral.

REDACTED Professor of Epidemiology and Health and Society at the Master of Public Health Program, Autonomous University of Santo Domingo.

REDACTED Epidemiologist, National Maternal and Child Health Research Center.

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Other Current Appointments

Professor of Epidemiology, Department of Public Health, The Autonomous University of Santo Domingo.

Honors

Dr. Fernando Alberto Defillo Award REDACTED

Cum Laude Graduate REDACTED

Fullbright-LASPAU Scholar REDACTED

Publications

Mendoza H, Bautista L, Montero R, González J: Sarampión en el Hospital de Niños Robert Reid Cabral y los efectos de la campaña de vacunación de 1985. Bol Unidad Estud Espec 1:3, 1986.

Mendoza H, Bautista L, Montero R, González J: Difteria, tétanos y tosferina en el Hospital de Niños Robert Reid Cabral y los programas de vacunación de SESPAS. Bol Unidad Estud Espec 1:6, 1986.

Bautista L, Montero R: Algunos aspectos epidemiológicos de las quemaduras en el Hospital de Niños Robert Reid Cabral 1981-1985. Bol Unidad Estud Espec 1:10, 1986.

Bautista L, Montero R: Morbimortalidad por enfermedad diarreica aguda en menores de 5 años de la Ciudad de Santo Domingo (1986). Informe final. Bol Unidad Estud Espec 2:7, 1987.

15.a HUMAN SUBJECTS

Recruitment and Consent

A cohort of 200 children under 2 years exposed to charcoal-smoke and a similar number of non-exposed will be selected from the population of children in Santo Domingo, Dominican Republic.

The mother and/or father of a child selected for the study will be approached at their home by a trained interviewer who will explain to them the nature of the study, its potential risks and benefits, and their right to withdraw from the study at any time. The interviewer will ask them to consent for their child to be included in the study and, if agreed, to sign an informed consent form. A copy of the consent form will be provided to the parents. In the absence of one parent, the consent of the other parent will be sufficient to consider the child as part of the study. Consent of the absent parent will be requested at the first opportunity.

Children found to be have moderate or severe ARI will be referred to a medical facility for pediatric care. Medical care and treatment is free of charge and easily available for this population.